THE YEAR BOOK *of* MEDICINE

(1956 1957 YEAR BOOK *Series)*

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THE PRACTICAL MEDICINE YEAR BOOKS

Thi volume is one of the 13 comprising the Practical Medicine Series of Year Books founded in 1900 by G P Head MD and C J Head and published continuously since then The complete li t follows

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DEPARTMENTS *of the* YEAR BOOK *of* MEDICINE

Infections

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The articles abstracted herein are taken from journals received between May 1955 and May 1956

PART I

INFECTIONS

PART II

THE CHEST

PART III

THE BLOOD AND BLOOD FORMING ORGANS

PART IV

THE HEART AND BLOOD VESSELS AND THE KIDNEY

INFECTIONS



PAUL B BEESON MD

PARI I

INFECTIONS

CHEMOTHLRAPY OF INFECTION—GENERAL

Causes of Failure in Antibiotic Therapy Chester W Howe[1] (Boston Univ) outlines some of the common types of failure and discusses the physiologic pathologic bacteriologic and clinical reasons related to cause and prevention

Empiric treatment of fever or other undiagnosed disease—An elevated temperature may accompany neoplasms hematomas lymphomas leukemias viral infections the normal postoperative state and other conditions in which antibiotics are ineffective If an infectious disease is impending but not yet manifest diagnosis may be delayed by institution of antibiotic therapy before material is obtained for bacteriologic culture Empiric antibacterial treatment sometimes results in temporary improvement of an undiagnosed condition as in carcinoma of the lung or gastrointestinal tract where superimposed infection so often occurs In malignant disease such delay might be fatal

Alterations in bacterial flora and superinfections—A new disease of different bacterial etiology—a superinfection—may actually develop during antibiotic treatment Hemophilus influenzae Escherichia coli Aerobacter aerogenes Pseudomonas aeruginosa various strains of neisseria Proteus vulgaris Klebsiella pneumoniae and monilia are present in only small numbers before therapy but become apparent or predominant after penicillin therapy

The organs oftenest involved by superinfection are most frequently the same ones affected in the primary disease but the responsible organisms are often difficult to treat with available drugs Exact incidence of superinfections in surgery is undocumented but an increasing number of patients previously treated with a variety of antibiotics have soft tissue and bone infections that yield pure cultures of Ps aerugi

(1) M Cl N th A 39 1351 1365 Sept mbe 1955

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nosa proteus Staphylococcus aureus or monilia resistant to the commonly used antibiotics

Futile prophylaxis—Perhaps 60% of all hospitalized patients and many at home receive antibiotics Cures are frequent and gratifying but the economic waste is enormous and after effects may be detrimental or dangerous rather than beneficial Use of antibiotics when unnecessary contributes to the increasing number of resistant bacteria Better selection of cases and control of treatment will minimize these undesirable aspects Much of the wastage is carried out as so called prophylaxis intended to ward off possible respiratory complications or other infections in patients with incipient coryza or after surgery

Under certain circumstances prophylactic chemotherapy is valuable e g penicillin in streptococcic pharyngitis and acute gonococcic urethritis contacts and for prevention of rheumatic fever recurrence Sulfadiazine prevents bacillary dysentery and meningococcic meningitis in exposed persons To prevent endocarditis use of prophylactic antibiotics would seem reasonable in patients with organic heart murmurs during operations or manipulations that might result in transient bacteremia in procedures in the presence of sepsis or in dental extractions Improved results in suppurative lung disease after surgery in recent years is in part due to use of prophylactic therapy Use of intestinal antiseptics before large bowel resection or ureterointestinal implantations has been successful in reducing complications

The most important prophylactic measure in treatment of contaminated wounds is thorough surgical *debridement* Antibiotics have not proved effective in preventing infection in a contaminated wound and if used at all should be used postoperatively Penicillin is the drug of choice because the flora usually responsible for wound infection hemolytic streptococci and clostridia are susceptible to it

If antibiotic prophylaxis in surgery were limited to these situations failure wastage and potential harm would be insignificant Though there is no evidence that penicillin prevents postoperative wound infection in clean civilian surgery many surgeons use antibiotics routinely after all operations clean or potentially septic

Penicillin is frequently given routinely after and before

surgery in an attempt to prevent pulmonary complications but atelectasis is by far the commonest complication and—whether it is called bronchitis atelectasis or bronchopneumonia—*is the result of mechanical factors* and is not primarily an infectious process Dried bronchial secretions mucous plugs muscle splinting and diminished aeration are primary factors Prevention depends on intratracheal suction and adequate pulmonary ventilation and not on antibiotics Only in the presence of atelectasis or stasis does infection occur If prevention fails and atelectasis develops the *infection may be caused by an antibiotic resistant organism* if the patient has received prophylactic antibiotics In the untreated patient it is usually one or more of the normal constituents which may be susceptible to antibiotics

Inaccessible lesions and untreatable entities—Chronic or recurrent sepsis produces fibrosis or scar tissue and is difficult to reach with an optimal concentration of antibiotic because of decreased *flow of blood and lymph to it* Abscesses sinuses chronic lesions with pockets of sepsis fibrosis granulation and scar tissue are not cured by either systemic or local chemotherapy

Therapeutic failure is sometimes attributed to an antibiotic when a disease such as ulceration of the extremities in peripheral vascular disease is not primarily infectious Any *open wound will harbor bacteria but often the* organisms are noninvasive saprophytes and not important in the etiology of the ulcer The infectious and vascular components of obliterative arterial disease are separate entities and the treatment is different

Miscellaneous causes of failure—Deficiency in host defenses may cause failure for an otherwise effective antibiotic *notably in agranulocytosis and leukemia Correction of* fluid and electrolyte imbalance and of nutritional vitamin and protein deficiencies and control of deranged physiology such as diabetes mellitus are necessary for successful antibiotic therapy

For some family physicians under pressure use of antibiotics empirically without prior Gram stain or culture may occasionally be justified Certain infections can be readily diagnosed clinically and are known to be uniformly susceptible to antibiotics *Facilities for an ordinary Gram stain*

should be available in every office for doubtful cases. If it does not seem worth while to perform this simple procedure before giving an antibiotic, indication for giving it at all should be seriously questioned.

The laity must be educated to the dangers of antibiotic therapy and the necessity of intelligent control. Every physician should be an active crusader for rational use of antibiotics whenever undue pressure is applied by a patient or relative for premature use.

Study on Penicillin Toxicity in Guinea Pigs was made by P. De Somer, H. Van De Voorde, H. Eyssen and P. Van Dijck. The lethal effect of small doses of penicillin in guinea pigs has been reported by several authors. Many suggestions including allergy and possible deficiency state have been made to explain the toxicity.

When penicillin in doses of 5 000 units was given intraperitoneally, mortality was 60-70%; with doses of 100 000 units it rose to 90%, but survival time was not appreciably shortened. Toxicity of penicillin in the guinea pig is a phenomenon similar to that of staphylococcic enteritis in man after broad spectrum antibiotics orally or intravenously. The normal gram negative and gram positive intestinal flora of man is suppressed by the antibiotic and the resistant staphylococci overgrow *the whole intestinal tract*, leading to fatal toxemia.

In guinea pigs the same thing happens. The normal gram *positive intestinal flora is inhibited soon after penicillin*, chlortetracycline or bacitracin is given. The gram negative bacilli overgrow other organisms of the intestinal tract, secreting toxins *that paralyze the normal intestinal peristalsis* and lead to obstipation and loss of appetite. The animals neither eat nor defecate for 24 hours after penicillin administration. In all probability the toxins of Escherichia coli are responsible.

• [*The unique susceptibility of the guinea pig to penicillin had never before been explained. The evidence presented here provides at least a very satisfying hypothesis.*—Ed.]

Blood Levels from Orally Administered Penicillins G and V: Relation to Food Intake. Wilfred F. Jones, Jr. and Maxwell Finland[3] (Harvard Med. School) determined the peni

(2) Antibiot. & Chemother. 5: 463-469, September, 1955.
(3) New England J. Med. 253: 754-761, Nov. 3, 1955.

cillin activity in plasma after oral penicillin V compared with similar doses of penicillin G Penicillin V (phenoxy methylpenicillin) is stable at pH ranges below 3 it has little solubility at acid ranges but can be converted to a water soluble alkali salt at a neutral or alkaline pH It differs from penicillin G by a single oxygen molecule but has significant ly different physical properties Preliminary clinical trials in Germany and Austria showed it to be a practical oral therapeutic agent particularly in children and apparently effective in susceptible infections

Single tablets of 200 000 units of penicillin V produced higher and more prolonged levels of plasma penicillin than did penicillin G judged by the antistreptococcic and anti staphylococcic activity of the plasma This was particularly striking if the doses were taken after breakfast Useful levels may be sustained by oral administration of penicillin V at four hour intervals

Penicillin V may be superior to penicillin G for oral use in prophylaxis and treatment of appropriate infections Fur ther clinical trials are indicated

Re evaluation of Sulfonamide Therapy is presented by El lard M Yow[4] (Baylor Univ) Interest in sulfonamides de creased after the introduction of penicillin because unlimited amounts of the antibiotic could be given without evidence of toxicity Since 1949 the increased experience with the newer sulfonamides has provided a basis for an evaluation of their indications

The sulfonamides are the preferred antimicrobial agents for meningococcic infections No clinically resistant strains of meningococci have been encountered Sulfonamides are as effective as tetracycline in bacillary dysentery and chan croid and probably as effective as any other antibacterial agent in anthrax cholera glanders plague inclusion con junctivitis and South American blastomycosis According to one report trachoma is best treated with sulfonamides They are generally effective in a large group of infections of the urinary and respiratory tracts

Because of their diffusibility and additive antibacterial ef fect sulfonamides are often of definite value when combined with antibiotics They are as effective as any other single

(4) A I t M d 43 3 3 332 A gust 1955

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(4) A I t M d 43 3 3 332 A gu t 1955

agent in infections due to anaerobic and aerobic actinomyces and probably more effective when combined with penicillin or iodides The author gives both penicillin and sulfonamides until cultures become negative Sulfonamide therapy is then continued for a month after all sinuses have stopped draining

New antibiotics will probably not be developed as rapidly as micro organisms adapt to them A possible solution to the problem of rapidly increasing resistance to the antibiotics is to reserve the most potent agents for serious illness and for those resistant to sulfonamides The average cost to the patient for sulfonamide therapy is about 50 cents a day compared with $2 00 for the tetracycline antibiotics

Sulfonamides produce undesirable side effects in about the same frequency as the antibiotics They are less potent antibacterial agents than the antibiotics but they also produce less drastic changes in the normal flora of the body and subsequent superinfections are minimized

• [True enough we don t see many articles about the sulfonamides now but I understand the number of tons made and sold in the United States continues to increase As with the antibiotics we are using much more than we should —Ed]

Nitrofurantoin Clinical and Laboratory Studies in Urinary Tract Infections are reported by William A Richards Egon Riss Edward H Kass and Maxwell Finland[5] (Boston) Nitrofurantoin a furan derivative is the first of this series of compounds to be used in human infections After oral administration it appears in significant concentrations only in the urine and its usefulness has thus been limited to urinary tract infections Useful levels have not been attained in the blood by oral therapy The levels determined by antibacterial action were comparable to those obtained by a spectrophotometric method Solubility increases with increasing pH At pH 4 0 solubility is 22 mg and at pH 7 0 and 7 7 it is 90 and 230 mg /100 ml

Nitrofurantoin 100 200 mg four times daily for 2 13 days (average 7 days) was given to 39 hospitalized adults with urinary tract infections Toxic effects were minor usually consisting of nausea and vomiting and in only 2 patients were they severe enough to stop medication though they occurred in 11 Sensitivity reactions were not noted but have been reported by others

(5) A.M A Arch Int. Med 96 437 450 Oct ber 1955

Favorable clinical effects were obtained in most acute and uncomplicated infections but in only a small proportion of chronic cases with underlying complicating conditions in the urinary tract The most favorable results were in Escherichia coli and gram positive cocci infections Infections with pseudomonas were not affected and new strains frequently appeared as new invaders In aerobacter infections results were intermediate Proteus strains were temporarily inhibited but usually not completely cleared and they sometimes appeared as new invaders during or promptly after therapy

• [It must be stressed that this drug is of value only as a urinary antiseptic Although clinical laboratories sometimes include it routinely in *sensitivity tests the concentration in other body fluids is so low that an* antibacterial effect would be unlikely except in the urinary tract—Ed]

Bacterial Sensitivity to Erythromycin Two Year Experience (1953 54) is reported by S Stanley Schneierson[6] (New York) The scope and effectiveness of each new antibiotic have been limited by development of resistance to its action by bacterial species originally sensitive to it Micro organisms isolated at the hospital from blood urine cerebrospinal fluid abscesses and purulent exudates sputum nose and throat and other sources were tested for sensitivity to erythromycin Sensitivity results were analyzed to ascertain whether changes had occurred in the susceptibility pattern of any bacterial species as expressed by relative increase in percentage of resistant strains

During the two years all cultures of Staphylococcus albus Streptococcus viridans beta hemolytic streptococcus and *pneumococcus except an occasional moderately resistant or* resistant strain were sensitive to erythromycin The percentage of erythromycin resistant strains increased slightly and progressively with passage of time but the changes were not statistically significant Most strains of Staph aureus and Str faecalis isolated from clinical material remained sensitive to erythromycin

Erythromycin resistant strains of Staph aureus were obtained chiefly from wounds and purulent exudates and those of Str faecalis from the urinary tract Together these sources provided about 80% of all erythromycin resistant strains of bacteria isolated during the entire time

• [In hospitals where erythromycin has been employed extensively a

(6) J Mt S [illegible] H p 22 1 5 M y Ju 1955

significant increased incidence of resistant strains has been observed since this is an antibiotic against which resistance develops frequently and quickly Because of that there has been a tendency to (1) reserve it for certain serious infections especially those due to staphylococcus and (2) always give another antibiotic with it to delay the emergence of erythromycin resistant strains —Ed]

Recent Studies on Albomycin a New Antibiotic manufactured during recent years in the Soviet Union was reported by G F Gause[7] (Moscow) Obtained from a new species of streptomycetes *Actinomyces subtropicus* albomycin inhibits gram positive cocci chiefly pneumococcus and staphylococcus and is effective against a number of gram negative bacteria including the coli dysentery group and Friedlander s bacillus Staphylococcus is inhibited by pure albomycin in a dilution of 1 700 000 000 contrasted to 1 80 000 000 required of crystalline penicillin a ratio of about 1 10 *Albomycin is practically nontoxic in animals and man* It appears to be a cyclopeptide with a molecular weight of not less than 1 300 and contains seven amino acids

The mechanism of action is bacteriostatic under aerobic conditions only The lack of toxicity of albomycin can be compared to that of penicillin The lethal dose could not be determined in mice rabbits cats or guinea pigs After subcutaneous *injection of 100 000 units/kg body weight into* rabbits the antibiotic was found in the blood for three days It protected mice against pneumococci staphylococci hemolytic streptococci dysentery bacilli and Friedlander s bacillus but was ineffective against tubercle bacilli listerella salmonella and rickettsia

Clinically albomycin has been used mainly against pathogenic cocci relapsing fever peritonitis and surgical infections Intrathecal injections have given good results in men *ingitis caused by penicillin resistant pneumococci*

• [This agent is not to be confused with albamycin® (novobiocin) which has recently been released for general use in the United States The Russian antibiotic sounds good indeed although I am somewhat puzzled by the last statement since penicillin resistant pneumococci don t seem to be found on this side of the *Iron Curtain* —Ed]

Apparent Activation of Salmonella Enteritis by Oxytetracycline is reported *in a patient by* Donald Finger and W Barry Wood Jr[8] (Washington Univ) A common complication of antibiotic therapy *is secondary infection of the*

(7) Brit. M J 2 1177 1179 Nov 12 1955
(8) Am J Med. 18 839 841 May 1955

mouth and gastrointestinal tract by micro organisms ordinarily of low pathogenicity the commonest secondary invaders being monilia and gram negative bacilli in the oropharynx and staphylococci in the esophagus and bowel Presumably the antibiotic has disturbed the normal micro flora of the mucous membranes In the present patient a pathogenic species of salmonella apparently carried in the bowel became activated during a course of prophylactic chemotherapy

Man 53 hospitalized for surgical repair of Dupuytren s contracture was given 250 mg oxytetracycline orally four times daily beginning the day of surgery On the 3d postoperative day he had a severe shaking chill and temperature was 103 8 F Oxytetracycline was discontinued and 250 mg tetracycline four times daily was begun On the 4th day the abdominal pain localized in the right lower quadrant and stools became frequent and loose with occult blood Temperature rose to 104 7 F and rigidity and tenderness were noted in the right lower quadrant Tetracycline was discontinued Within 24 hours abdominal pain decreased and after 48 hours he was afebrile Diarrhea rapidly subsided and stools became firmer Stool cultures on the 4th 5th and 6th days revealed Salmonella muenchen resistant to tetracycline

Experimental work that has a direct bearing on the phenomenon observed has been reported The microflora of the gastrointestinal tract of mice pretreated with streptomycin was profoundly affected and the mice became highly susceptible to orally induced infection with the salmonella strain Normally mice are resistant to these salmonella

Postoperative salmonella infection in man is so rare that salmonella enteritis in this patient was most likely due to the antibiotic therapy rather than to the operation

• [First of all was the postoperative chemoprophylaxis necessary? Of more general interest of course is that this appears to be a clear instance of an unusual kind of superinfection and to be a demonstration in man of a phenomenon previously described by Miller in mice —Ed]

Present Status of the Antimalarial Drugs Chloroquine Pyrimethamine (Daraprim) and Primaquine is reviewed by G Robert Coatney[9] (Nat l Inst of Health) Chloroquine has distinctive pharmacologic properties which must be understood to realize its full potentialities Absorption from the gastrointestinal tract is rapid and almost complete The drug is concentrated in the tissues in amounts up to 500 times those in plasma This tissue affinity plus the fact that

(9) I d t & T p Health 2 116-1 1955

the drug is slowly metabolized and slowly excreted allows blood levels to remain high enough to suppress completely malarial attacks for six weeks or longer after administration has been stopped The antimalarial activity of chloroquine depends on the concentrations in the plasma Therefore to obtain rapid therapeutic effectiveness loading doses should be used

Toxicity due to chloroquine is extremely low at the doses recommended for suppression or for therapy The antimalarial effect of the drug is due largely to its action against erythrocytic parasites This activity is greater and more dependable than that obtained with any other drug Chloroquine does not prevent infection with any of the human malarias and does not prevent or destroy the late tissue forms of Plasmodium vivax

Single weekly doses of 300 mg (base) will completely suppress all species of malarial parasites in the circulating blood An acute attack is effectively treated by 600 mg *(base) in a single dose followed in six hours by 300 mg* and then 300 mg on each of two successive days for a total of 1 500 mg (base) in three days Fever is generally eliminated within 24 hours and the circulating parasites disappear within 48 72 hours So far no chloroquine resistance has been demonstrated The periods of latency are longer than with any other drug The skin and eyes are not stained and the drug ordinarily produces no undesirable side reactions

Pyrimethamine (daraprim®) in small weekly doses of 25 mg completely suppresses all the malarias Suppressive cure against P falciparum and certain strains of P vivax is possible The drug has a lasting adverse effect against gametocytes It is tasteless an especially important feature in treating infants and children and is relatively inexpensive Its limitations are slowness of action in acute attacks and the possibility that certain strains of malarial parasites may become resistant Resistance can be prevented by administering adequate doses for therapy or suppression

Pyrimethamine and chloroquine are useful primarily in suppressing or treating an overt attack The 8 aminoquinolines however destroy the exoerythrocytic parasites and can radically cure the *infection Pentaquine was found to be* lethal to gametocytes of all species of malaria but too toxic

for human use Primaquine is the most active and best tolerated of the 8 aminoquinolines Amounts sufficient for cure can be given in single daily doses Primaquine will probably replace all other 8 aminoquinolines for the cure of relapsing malaria

Plasmodium vivax infections can be eradicated For an acute attack chloroquine should be started immediately and primaquine therapy instituted concomitantly or shortly afterward with 15 mg single daily doses for 14 days Against certain strains of vivax a second course may be necessary If the patient has left the malarious area and infection is known or suspected primaquine may be given in the same manner but chloroquine omitted

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CHEMOPROPHYLAXIS OF INFECTION

Chemoprophylaxis of Infection is reviewed by Louis Weinstein[1] (Boston Univ) Chemoprophylaxis in some infectious diseases is based on studies which have confirmed its usefulness but in others it has not been subjected to adequate and controlled investigation Most commonly it has been used in healthy persons to prevent invasion by specific bacteria

Administration of chemotherapeutic agents preferably penicillin to persons exposed to invasion by beta hemolytic streptococci affords predictable good protection Penicillin is also highly effective in healthy persons exposed to gonorrhea Sulfonamides are the most effective agent for preventing bacillary dysentery

One of the commonest prophylactic uses of antibiotics has been in undefined viral diseases of the upper respiratory tract Attempts to prevent secondary infections have not been successful Regardless of the prophylactic program invasion by all organisms cannot be eliminated The etiology of the complications may be altered but their incidence may be little if at all changed Despite its lack of success prophylaxis is still widely used in most viral respiratory diseases

Antibiotics have often been given in childhood diseases to prevent secondary bacterial infections In a recent study

(1) Ann Int Med 43 87 298 August 1955

of chemoprophylaxis in measles the incidence of secondary infections was higher with than without antibiotics

Antimicrobial agents have also failed to protect against bacterial invasion in respiratory poliomyelitis Of 165 patients with bulbar involvement or paralysis of respiratory muscles who received no antibiotics 16% had secondary infections Of 63 given chemoprophylaxis 53% had bacterial complications an increase of about 3 5 times Although the more seriously ill patients were most often treated prophylaxis still failed to protect those who needed it most Pneumonia occurred in 22% of the patients given chemoprophylaxis and in only 6% of those not receiving antibacterial agents In the treated patients the commonest causative agents were Pseudomonas pyocyanea penicillin resistant Staphylococcus aureus and Hemophilus influenzae in the untreated group pneumococcus and beta hemolytic streptococcus were most often found

In many hospitals antibiotics are given to patients with heart failure coma cerebrovascular accidents or shock to prevent bacterial infections Little or no conclusive evidence substantiates their usefulness Such patients are susceptible to bacterial invasion and are exposed to the risk of superinfection if given antibiotics Complete prevention of infection is impossible despite use of potent drugs alone or in various combinations

The same untoward reactions occur when antibiotics are given therapeutically or prophylactically Allergic episodes varying from mild skin rashes to fatal attacks of acute anaphylaxis reactions to the irritating and toxic properties of the drugs disturbances in metabolism and serious superinfections have occurred These risks are justified when the antibiotics are of proved value for protection against infection If their effectiveness is questionable the benefits to be derived must be weighed against possible dangers If there is no evidence that chemotherapy will be effective it should not be given

• [In this and the next article Weinstein presents some thought provoking arguments against the practice of chemoprophylaxis in such conditions as measles poliomyelitis coma etc We need more factual information of this kind —Ed.]

Failure of Chemotherapy to Prevent Bacterial Complications of Measles Secondary bacterial infection is the com

monest complication of measles Since previous reports of chemoprophylaxis concerned hospitalized patients though such treatment is usually given at home Louis Weinstein[2] (Boston Univ) investigated the influence of chemotherapy during pre eruptive and eruptive stages of rubeola on the number and type of complications at hospitalization

On admission 78 of 428 patients had superimposed bacterial disease Procaine penicillin or broad spectrum antibiotics alone or in combination had been given to 130 patients and of these 36 (30 4%) had secondary bacterial infections on admission Of 298 patients who had received no antimicrobial agents 42 (14 9%) had bacterial infections Of the 78 patients with bacterial infection on admission 36 (46%) had received an antimicrobial drug before infection developed

Secondary bacterial invasion occurred in 16 patients during hospitalization Pneumonia and suppurative otitis media were the commonest lesions and the most frequent bacteria were pneumococcus Hemophilus influenzae beta hemolytic streptococcus and Staphylococcus aureus These 16 patients and the 78 who entered with bacterial complications were all treated with antibiotics Of these 94 patients 11 (11 6%) showed a new infection during therapy due to monilia H influenzae Escherichia coli Staph aureus or proteus

Antimicrobial drugs during pre eruptive or eruptive stages of measles did not prevent secondary bacterial infections and may have increased the risk of their development Bacterial invasion was more than twice as frequent in patients treated than in those not treated before hospitalization and over seven times more frequent than in patients who received no chemoprophylaxis after admission Infections that occur during chemoprophylaxis may be due to drug resistant organisms As each antibiotic agent carries a risk of reaction it is not only unnecessary but unwise to administer chemotherapeutic agents to patients with rubeola until evidence of treatable secondary bacterial complication appears

(2) New Engl J Med 253 679 683 Oct 20 1955

CANDIDA INFECTIONS FOLLOWING ANTIBIOTICS AND CORTISONE

Effect of Nystatin on Growth of Candida Albicans during Antibiotic Therapy A J Childs[3] (Glasgow) treated 50 males over age 12 all of whom had pneumonia with tetra cycline Alternate patients received nystatin (mycostatin) 1 tablet (500 000 units) every eight hours

Most specimens from patients with pneumonia contain C albicans on hospitalization In the present study tetra cycline increased the number of specimens from which the fungus could be isolated and the increase gradually contin ued until the seventh hospital day two days after the anti biotic was stopped This was true of all regions examined In patients who received nystatin the yields tended to be lower but not uniformly so Heavy growths were eliminated from the rectum The effect in the throat was less obvious and sputum cultures were similar to those in controls

Nystatin appears to be most effective in the bowel less effective in the throat and without effect in the sputum A high local concentration is important for antifungal action in vivo Nystatin orally would be unlikely to control candida infection in sites reached only by the blood stream

Moniliasis of Mucous Membranes and Lungs as Complica tion of Treatment with Antibiotics Corticotropin and Corti sone is reported by Harriet Bratlund and C Holten[4] (Mun Hosp Aarhus Denmark) Candida albicans is often found on the mucous membranes as a saprophyte In the intact membranes it does not grow among the epithelial cells nor penetrate into underlying tissues Even in the presence of a mucous membrane lesion the fungi do not extend into deep er layers and do not produce disease They may however become virulent if tissue resistance is lowered or if they are present in overwhelming quantities Such a situation exists when antibiotics suppress other micro organisms but not the fungi The latter are resistant to all commonly used anti biotics

(3) B t M J 1 660 66 Mar 24 1956
(4) Da h M Bull 1 79-84 June 1954

In such conditions the white spots of thrush may become extensive They tend to disappear in three to four days but may persist for months extend over and even penetrate the mucous membranes and spread into the submucosa and into the vessels Metastases to distant organs can occur if the mycelium and spores are not destroyed in the blood or tissue fluids by antibodies or potent phagocytes

Of 210 patients treated with ACTH and/or cortisone 18 developed moniliasis Since records of all patients treated with these hormones are kept in a special register it was possible to trace all cases however slight Of the 18 patients 11 had mild moniliasis but in several it was troublesome and constituted a serious complication of the primary disease In three severe moniliasis involved the oral cavity pharynx and larynx and in two the lungs In two others generalized exanthema developed suddenly and was interpreted as monilid due to an allergic reaction caused by metabolic products of C albicans Of the 18 patients 8 had received hormone therapy without antibiotics Seven received hormones and antibiotic therapy simultaneously Three were given antibiotics alone They had been on ACTH or cortisone therapy previously but this treatment had been discontinued 3 weeks to 2½ months before signs of moniliasis appeared

This report serves as a reminder that treatment with antibiotics and with corticosteroids should be used only if unquestionably indicated

Thrush Septicemias (Candida Albicans) Favored by Antibiotics and Cortisone in Course of Malignant Hemopathies were observed in four adults by H Dubois Ferriere R Feuardent H Goldschlag L Burstein C Bouvier and H Bohni (Univ of Geneva) Two had acute leukemia one malignant reticulosis and one Hodgkin s lymphogranuloma All received cortisone and antibiotics and two also had antimitotics All four died of generalized candidiasis which took the form of hyperacute gastroenterocolitis in three and caused generalized septicemia in one Autopsy was performed in two

Proliferation of C albicans in the buccal cavity vagina and intestinal tract sometimes occurs in cachectic patients

(5) H l t med t 2 477 481 N mb 1955

Trousseau in 1869 *regarded this as a local manifestation* of a poor general state During the last 15 years it has been recognized that C albicans may be responsible for endocarditis meningitis, bronchopneumonia and true bacteremias capable, by *hematogenous dissemination of producing* abscesses in all parenchyma Such occurrences are attributed to systematic use of antibiotics which modify the intestinal flora and favor vitamin B deficiency thus creating optimal conditions for proliferation of thrush More recently prolonged use of cortisone and ACTH *has been incriminated* along with antimitotic drugs in children with acute leukemia

Recrudescence of fungous infections seems particularly to be feared in hemopathies because (1) bacteriologic examinations have improved and C albicans is more easily recognized (2) cachexia favors its dissemination and (3) therapy plays an obvious role The antagonism of fungi toward microbes on which action of antibiotics depends also acts in *reverse when the organism is depleted of bacteria by anti*biotic therapy Cortisone and ACTH facilitate dissemination of C albicans in the same way that they favor extension of bacterial infections Antimitotics (aminopterin and 6 mercaptopurine) play a similar role Finally hemopathy itself and especially neutropenia can be incriminated because no leukocytic reaction occurs in the neighborhood of foci of C albicans

Combined cortisone antimitotic and antibiotic treatment should not be used in hemopathies without due consideration and search for an efficacious fungicide should be pursued

• [Generalized moniliasis is rarely encountered except in patients such as these who during long debilitating illnesses have received antibiotics and cortisone or such drugs as aminopterin Nystatin doesn t seem effective against this kind of monilial infection —Ed]

CORTISONE IN TREATMENT OF INFECTIONS

Combined Hormonal *Antibiotic Therapy in Patients with* Fulminating Infections Laurance W Kinsell and John P John[6] (Oakland Calif) reviewed the findings in 300 pa

(6) A M A Arch I t Med 96 418-4 6 September 1955

tients Despite the efficacy of antibiotics patients still succumb to infectious diseases because of late diagnosis poor constitutional status or unusually virulent infections A significant number who have generalized peritonitis meningococcemia and other infections are hospitalized nearly moribund

Combined hormonal antibiotic therapy is based on the hypothesis that corticoids in some way exert a nonspecific antitoxic effect protecting the cells of the host against a variety of bacteria and toxins It was postulated that the corticoids *would keep the patient alive until proper therapy had sufficient time* to take effect and that the improved status would allow surgery if necessary

The first patient so treated was a child with generalized peritonitis after a ruptured appendix Despite antibiotics the condition was critical and corticoids were started In 24 hours the patient appeared clinically well peristalsis was active and a stool was spontaneously passed

Generalized peritonitis is now considered a specific indication for combined therapy Any bacterial infection of unusual severity for which a specific antibiotic is available is *a potential indication for intensive initial corticoid therapy* All patients with meningococcemia with or without meningococcic meningitis routinely receive combined therapy All patients with bacterial meningitides of more than usual severity if the organism is sensitive to specific antibiotics is treated with corticoids Bacterial infections of average severity should be treated with antibiotics alone except possibly infections of the central nervous system

Infections for which antibiotics are not available should not be treated with corticoids the two exceptions being severe viral hepatitis and mumps orchitis In general corti*coid therapy is contraindicated in patients with active tuber*culosis peptic ulcer or major emotional instability but in a critically ill patient any contraindication to any therapeutic agent is relative Corticoid therapy—emergency or not—should be avoided in patients with widespread long standing allergic dermatoses The incidence of complications in these patients has been disturbingly high

On the basis of this study it appears that in patients with severe systemic infections combined hormonal antibiotic

therapy may have lessened the morbidity and mortality Intensive corticoid therapy may result in rapid and profound diminution of systemic toxicity

• [Kinsell has been the most vocal champion of the use of corticoids in severe infection I occasionally give hydrocortisone to a critically ill patient in the hope of tiding him over the first 12 24 hours while appropriate antibiotic therapy is gaining time to take hold Occasionally it has seemed to be of value On the other hand many experienced clinicians are wholly opposed to this line of treatment The data presented in the following article indicate that it is not too risky —Ed]

Effect of Hydrocortisone on Course of Pneumococcic Pneumonia Treated with Penicillin Few animal experiments have been reported in which steroids were administered after infection had been established In several instances the toxemia of severe human infections has been reported suppressed by corticosteroids Henry N Wagner Jr Ivan L Bennett Jr Louis Lasagna Leighton E Cluff Miriam B Rosenthal and George S Mirick[7] report on 113 patients Each received 300 000 units of aqueous potassium penicillin G intramuscularly every 12 hours for 7 days or until he was afebrile for 48 hours In addition 52 randomly selected patients from this group each received a total of 560 mg hydrocortisone orally during the five days after hospitalization

Of the 113 patients 1 in the hydrocortisone treated and 1 *in the control group died No suppurative complications* such as empyema meningitis pericarditis etc occurred in any patient Pleural effusion developed in four receiving penicillin alone and in three receiving the two drugs The fluid aspirated from all seven patients was sterile and none required more than one thoracentesis None of the common complications of adrenal steroid therapy was observed In one patient receiving hydrocortisone who had pneumonia and hypotension on admission striking hypothermia and acute renal failure developed The fall in temperature was probably due to the adrenal steroids the renal failure probably was not

The most obvious effect of hydrocortisone was altered febrile response Of the 52 patients 50 became afebrile by crisis within 24 hours Characteristically temperatures fell sharply to slightly subnormal levels and rose to the base line normal as the dose was decreased Subjective improve

(7) B H. J hns H pk ns Hosp 98 197 15 Ma ch 1956

ment was more rapid by day to day evaluation in steroid treated patients but the time required for complete disappearance of symptoms was the same in both groups

In many experiments unequivocally initiation of infection in animals treated with corticosteroids accelerated the disease process and increased mortality causing some clinicians unjustifiably to conclude that steroids are contraindicated in human infections Disregarding entirely the critical factors of dosage and species variations in adrenal cortical secretion one can consider several aspects of management of infections in man (1) Patients present themselves for treatment after infection and illness are established and corticosteroids then may have quite a different effect than when given as premedication (2) In man therapy includes the proper antibiotic or chemotherapy which is given not once and in minimal amounts but repeatedly and many times the minimal curative dose (3) Several reports have indicated that corticosteroids given to patients with various types of infections usually with antibiotic or other specific treatment produce no disastrous complications and may be beneficial

The symptomatic benefit of hydrocortisone and absence of aggravation of pneumococcic pneumonia as shown by the study justify further cautious exploration of adrenal steroids as adjuvants to specific antimicrobial therapy

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STAPHYLOCOCCIC INFECTIONS

Current View on Problem of Drug Resistant Staphylococci and Staphylococcic Infection is presented by Vernon Knight and Harvey S Collins [8] The increase in resistance of staphylococci to antibiotics is undoubtedly a consequence of the use of antibiotics in treatment of infections Factors which control the development and distribution of drug resistant staphylococci in man and evaluation of the effect of drug resistance on human staphylococcic infections are important clinically

After the introduction of penicillin into clinical use the occurrence of penicillin resistant staphylococci increased

(8) B U N w Y k A d M d 31 549 568 A gu t 1955

greatly In 1945 Spink in Minneapolis found only 12% of 68 strains of staphylococci to be penicillin resistant but in succeeding years there was a regular increase in widely separated areas of the world The highest percentage reported was 88% in 1951 in hospital patients In contrast to hospitals carrier rates of resistant staphylococci in the general population has increased only slowly ranging from less than 10 to 32% from 1948 to 1951

After the introduction of chlortetracycline and oxytetracycline increasing numbers of staphylococci became resistant to them In 1950 only 4 8% of strains from hospital patients were resistant to these agents but by 1951 this had increased to 78% A high predominance of phage group III staphylococci resistant to multiple antibiotics was characteristic of hospital patients but probably not of the flora of non hospitalized persons in the same area

The mortality rate in staphylococcic infection associated with bacteremia is high because the disease often occurs in patients with diabetes arteriosclerosis neoplastic disease or other debilitating illness Though the mortality rate in staphylococcic infection was somewhat reduced by penicillin the percentage of fatalities is still substantial Some mortality might be attributed to drug resistance of infecting strains but the mortality in patients with penicillin susceptible infections and the survival of others with resistant strains suggest that other factors also influence the rate Treatment with erythromycin and other agents will salvage some patients but a considerable proportion will succumb despite all treatment

The present outlook for treatment of staphylococcic infections is not optimistic Before antibiotics the mortality rate of acute staphylococcic bacteremia was 66 80% With penicillin mortality was significantly reduced to 28 54% In the recent era with use of erythromycin and other drugs about half the patients have died despite intensive antimicrobial therapy

The mortality rate from acute staphylococcic bacteremia now is of the same general magnitude as that in the early period of penicillin therapy Drug resistance has not been an important cause of failure in treatment of staphylococcic infection Though many staphylococcic infections are caused

by drug resistant strains agents such as erythromycin—formerly tetracycline—are highly active against the strains which are resistant to penicillin or streptomycin When used against drug susceptible infections these agents have often been successful

To control drug resistant staphylococci in hospitals one or more agents should be limited in use until the staphylococci present in the environment have again become susceptible to them At present there is a fairly general and almost involuntary attempt not to use erythromycin in order to save its effect for staphylococcic infections

• [The first three articles in this section all deal with the serious situation we find ourselves in that the personnel of hospitals are frequently carriers of pathogenic antibiotic resistant staphylococci In a manner of speaking we seem to have a situation comparable to the hospital infections of pre Listerian days—serious staphylococcic postoperative infections are frequent and debilitated patients are being overcome by fulminating staphylococcic pneumonias What to do about it is the question One cannot enthusiastically endorse strict isolation of a patient with staphylococcic infection when it is assumed that three fourths of all the hospital personnel are carrying similar bacteria in their noses —Ed]

Epidemiologic Studies on Antibiotic Resistant Strains of Micrococcus Pyogenes are reported by Robert I Wise Caroline Cranny and Wesley W Spink[9] (Univ of Minnesota) Many reports from various parts of the world have emphasized the increasing frequency of penicillin resistant strains of staphylococci in hospital patients However the incidence has not increased in outpatients or persons unassociated with hospitals Apparently there is a high incidence of penicillin resistant strains of staphylococci existing in the nares and pharynges of members of hospital staffs and of hospital patients

Studies during the last decade indicate that the incidence of antibiotic resistant strains of staphylococci is directly related to the quantities of antibiotics administered to hospital populations As each antibiotic is extensively used in therapy the incidence of resistant strains of staphylococci rises for that antibiotic If the use of an antibiotic is curtailed as with chloramphenicol the incidence drops Bacteriophage typing has revealed a predominance of group III staphylococci isolated in infections caused by antibiotic resistant strains

(9) Am J M d 0 176 18 F b ry 1956

Because of a selective process of antibiotic action antibiotic resistant strains predominate in the hospital environment These strains are carried by patients and hospital personnel Highly resistant strains infect wounds cause pneumonia genitourinary tract infections and in some cases septicemia often fatal The nature and magnitude of this problem demand recognition Prophylactic measures are necessary to prevent cross infections in patients and establishment of the carrier state in members of the hospital staff

Coagulase Positive Staphylococci Serial Survey for Nasal Carriers during First Six Months of Nursing Training J Brodie T Sommerville and S G F Wilson[1] (St Andrews Univ) examined 30 student nurses weekly for six months The students spent three months in the preliminary training school of a general hospital and three months on ward duty

Frequency of coagulase positive staphylococci isolated increased after ward duties began *During preliminary training 73 of 274* specimens *(27%)* were coagulase positive staphylococci during ward work incidence was 133 of 234 specimens (57%) Sensitive strains decreased from 38 to 1 5% and cross resistant strains increased from 10 to 43% During the *three months training no evidence of cross infection* between nurses was noted On ward duty acquired infection undoubtedly is important

This study demonstrates that nurses become carriers of staphylococci after entry to the wards but more important the types of staphylococci are relatively small in number The nurse is clearly a potential source of infection but she contracts the infection during ward duties The infection is acquired by the nurse while she is taking care of patients

An index is necessary to measure extent of staphylococcic cross infection in a hospital The nurse nasal index for staphylococci disclo es the extent to which a hospital has been colonized by the hospital staphylococcus and should be useful in assessing methods of control

Staphylococcic Infection Following Cardiac Surgery is reported in nine patients by H A Fleming and R M F Seal[2] The infection followed mitral valvotomy in seven and liga

(1) Brit M J 1 667 669 Mar 4 1956
(2) Thorax 10 32 337 1955

tion of a patent ductus in two The patients were in four hospitals and were operated on by five different surgeons Three of the organisms isolated were the nonpathogenic coagulase negative variety

Staphylococcic endocarditis appeared within two to three weeks of mitral valvotomy and did not conform with the usual conception of bacterial endocarditis Clubbing splenomegaly Osler s nodes and changes in the optic fundi were absent and petechiae were most unusual Cardiac murmurs remained unchanged Absence of these features has been noted in spontaneous staphylococcic endocarditis also The only suggestive features in early stages are unexplained fever and lack of well being Later hectic fever and rapid deterioration in general condition possibly with anemia and jaundice progressing to mental confusion and incontinence with death in coma ensue Symptoms and signs may be attributed to pulmonary infarction and may distract attention from the infective nature Presumed pulmonary infarction was treated with anticoagulants in five of the patients

In the four patients successfully treated with antibiotics blood culture was positive during the early stage of general malaise and unexplained fever If the appropriate drug can be administered at this time the disease can be quickly controlled

Pathogenesis depends on local operative trauma and opportunity offered for entry of organisms The importance of these two factors is difficult to evaluate particularly in individual cases

Of the nine patients five died two of endocarditis after mitral valvotomy and two of rupture of a false aneurysm of a ligated ductus One died unexpectedly and suddenly of myocardial abscess after mitral valvotomy

Diagnosis after mitral surgery can be made in early stages when fever and failure to do well are the only features blood cultures are positive at this stage Chest pain with hemoptyses high fever anemia jaundice and mental changes were the salient features False aneurysm formation of the ligated ductus was signaled by increasing radiologic opacity and repeated hemoptyses with fever Coagulase negative staphylococci may be pathogenic in endocarditis

• [The surprising thing is that endocarditis has not been a more fre

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quent complication of cardiac valvular surgery since cutting or tearing a valve is one of the old methods of producing bacterial endocarditis in animals —Ed]

Staphylococcic Endocarditis after Mitral Valvulotomy Report of Three Cases due to an antibiotic resistant Staphylococcus aureus is presented by John C Dalton Bryan Williams and Leonard Atkins[3] (Harvard Med School) who again call attention to this infrequent but serious complication of commissurotomy and the continuing hazard of infection with antibiotic resistant micrococci

CASE 1 —Man 36 was seen two months after surgery because of continuous dull nonpleuritic pain in lower thorax and dyspnea for two days On the previous night he had had a brief shaking chill with temperature rise to 101 F Blood cultures yielded Staph aureus He died five months after surgery

CASE 2 —Woman 44 became febrile two weeks after surgery Three weeks later coagulase positive Staph aureus was cultured from the blood She died four days later

Case 3 —Woman 42 did well for about 3½ months after mitral valvulotomy when she began feeling generally unwell Staph aureus was cultured from the blood She died 1 month later 4½ months after surgery

Bacterial endocarditis after cardiac surgery is not common In two reported series totaling 600 cases none was reported The authors three patients are from a group of over 150 who had mitral valvulotomy since 1951 Two of the three received penicillin immediately after surgery and in all the staphylococcus recovered was penicillin resistant Postoperative infections with antibiotic resistant staphylococci are an increasing hazard

No definite clinical picture has been observed Onset has varied from two days to three months postoperatively Staphylococcic endocarditis is usually regarded as an acute febrile illness heralded by sudden onset of chills and fever but there may be a period of subacute nonspecific symptoms and low grade fever Absence of petechiae and of a palpable spleen has been noted and their absence does not exclude the possibility of staphylococcic endocarditis

(3) New England J Med 254 205 10 Feb 2 1956

CLOSTRIDIAL INFECTIONS

Postabortal Clostridium Welchii Sepsis with Massive Hemolysis Report of Case is presented by Robert L Isham and Stuart C Finch[4] (Yale Univ) Most reviews of this subject have appeared in the obstetric literature as most of these patients are admitted on obstetric services Generalized sepsis may be so pronounced that the nature of the underlying process is obscure Tentative diagnosis in this patient was hemolytic anemia of undetermined cause

Negress 28 divorced had vaginal bleeding two days before hospitalization Several hours later she had severe epigastric pain which became generalized nausea vomiting and diarrhea with 10 15 watery stools a day She had shaking chills severe generalized muscular aching and the scleras were brown The abdomen was diffusely and exquisitely tender Blood was present in the vagina and a small amount of necrotic tissue protruded from the cervical os The uterus was tender She had generalized muscular tenderness

Dark brown guaiac positive urine contained 4+ albumin Hematocrit value was 26% and leukocyte count was 65 000 Reticulocyte count was 2% Cold agglutinin sickle cell lupus erythematosus and Coombs antiglobulin test results were negative Sternal marrow aspiration disclosed moderate erythroid hyperplasia A buffy coat smear showed many phagocytized erythrocytes The plasma was the color of port wine and spectroscopic examination showed both methemalbumin and oxyhemoglobin present Osmotic fragility was significantly increased Blood cultures grew Streptococcus faecalis sensitive to penicillin and to the tetracyclines A cervical culture grew Proteus vulgaris Str faecalis and Cl welchii and urine culture grew P vulgaris and Cl welchii

Within three hours of hospitalization the hematocrit value had fallen from 26 to 15% Parenteral fluids and blood transfusions raised the hematocrit to 23% Penicillin and streptomycin were given Diarrhea stopped but myalgia and abdominal pain persisted A large amount of foul bloody necrotic material was removed from the uterus and a small amount of gas was observed bubbling from the cervical os

During the next several days she remained alert and comfortable Fluid intake was kept between 600 and 900 ml of 20% dextrose in water daily Weight remained constant and edema did not develop On the eighth hospital day the serum potassium rose to 7 6 mEq /L and she died the next day

Autopsy revealed acute necrotizing parametritis congestion of the liver spleen and kidneys severe swelling of the kidneys and gener

(4) New England J Med 254 317 3 0 Feb 16 1956

alized icterus Postmortem cultures from the endometrium were positive for Cl welchii

Clinically the septic patient is alert and has a feeling of relative well being Fever is often low and is an unreliable index of severity of disease The pulse is rapid Physical findings are moderate to severe muscle tenderness and obvious icterus Laboratory findings invariably reveal elevated leukocyte count thrombocytopenia and anemia Hemolysis is frequently severe in such cases lower nephron nephrosis develops Most patients have a mixed uterine infection and culturing Str faecalis from the blood in this case was not surprising Often clostridia cannot be cultured from the blood

Treatment of the authors patient was chiefly management of renal failure The infection was adequately controlled with penicillin and hemolysis did not occur after the first day

Certain hematologic features of this case should be emphasized Massive intravascular hemolysis was indicated by the profound and rapidly progressing anemia and by free hemoglobin and methemalbumin in the plasma Microspherocytes were present On the day after antibiotic and transfusion therapy was begun most of the circulating red cells were abnormally sensitive to hypotonic saline solution This was less marked on the following day and within two days osmotic fragility had returned almost to normal The extensive erythrophagocytosis in the buffy coat smears also demonstrated presence of damaged coated or altered cells Despite massive hemolysis reticulocytosis did not occur and the hematocrit value did not improve Lack of expected erythropoietic response was probably due to progressive azotemia and smoldering infection

• *[I saw this patient and can testify that immediate recognition of the* diagnosis was not easy since at the time of hospitalization the dominant feature was severe hemolysis the hematocrit value falling from 26 to 15 in the first three hours Fever and abdominal pain are of course not at all uncommon in acute hemolytic episodes The syndrome is easier to recognize if it is known that an abortion has occurred —Ed.]

Purulent Clostridium Welchii Meningitis Originating from a Penetrating Cranial Wound Report of Case Cured with Penicillin and Anti Gas Gangrene Serum is made by Bent Møller[5] (Randers Denmark)

(5) A ta ch s d v *109 395 399 1955*

Boy aged 22 months had fallen backward and hit his head against a garden rake 36 hours before hospitalization Tetanus antitoxin had been given immediately without adequate local treatment. He became febrile and listless vomited repeatedly and had diarrhea On admission the occipital area contained a palm sized edematous swelling containing a little brown thin fetid pus Lumbar puncture revealed purulent cerebrospinal fluid containing 115 000 cells/cu mm and gram positive rods

Treatment was instituted with dipenicillin (400 000 units subcutaneously daily) and dihydrostreptomycin Six hours later mental status had cleared completely and he reacted normally Roentgen examination of the skull revealed no gas bubbles but slight crepitation was elicited by palpating the edematous swelling The wounds were debrided under local anesthesia 12 hours after admission 48 hours after injury Abundant thin pus escaped and two small perforations leaked cerebrospinal fluid Anti gas gangrene serum (40 ml) was given The general condition remained good but because of the nature of the infection he was given 75 ml blood intraosseously three days after admission Temperature fell to normal by the eighth day

Cultures of the wound pus grew Cl welchii and yellow hemolytic colonies of staphylococci

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SALMONELLA INFECTIONS

Salmonellosis Originating in a Hospital A Newly Recognized Source of Infection An epidemiologic study was made by Lawrence J Kunz and Orjan T G Ouchterlony[6] (Harvard Med School) During a three month period salmonella infections were sustained by five patients Each had been fed by stomach tube Dietary personnel appeared exonerated because the tube feeding formulas were prepared in two separate kitchens The most likely responsible ingredients were dried inactive yeast and dried milk solids and these were studied bacteriologically Three salmonella species were isolated from the dried inactive yeast S senftenberg montevideo and oranienburg Although not sterile the dried milk solids contained no salmonella organisms

The manufacturer immediately undertook an investigation of the yeast processing plant and discovered that the micro organisms were introduced from the outside air into the building by a ventilating duct Recognition of this source

(6) N w E gl d J M d 53 61 763 N 3 1955

suggests that other food products similarly processed should be closely scrutinized bacteriologically

Epidemic Due to Salmonella Typhimurium (Breslau) Occurring in Sweden in 1953 With Special Reference to Clinical Complications Bacteriology Serology Antibiotic Treatment and Morbid Anatomy The epidemic arose from meat contaminated by S typhimurium in a slaughterhouse There were 8 569 cases reported between June 15 and Dec 31 1953 In Stockholm about 900 patients were hospitalized and 654 of these with infection verified bacteriologically or serologically were studied by Elias Bengtsson Per Hedlund Åke Nisell and Hans Nordenstam[7] Of the 309 males and 345 females 136 were under age 15 and 44 over age 65

Of the 654 cases 43 were severe and 156 moderate the other 75% being mild Of children under 15 only 2 were severely affected in old people the reverse was true and of 16 aged patients gravely ill 7 died On the average duration was one week for mild and two for moderate or severe cases

Predominant clinical symptoms were fever diarrhea and vomiting Nearly all patients had violent diarrhea usually lasting four to six days and in 138 persisting for one to two weeks The white blood cell count was usually normal but in 12% was less than 4 000/cu mm

Complications included thrombosis thrombophlebitis and cystopyelitis in 18 patients and pneumonia in 6 Blood cultures were positive in only 5 of 159 patients Osteomyelitis in one of the cuneiform bones was seen only once in a woman aged 28 All severely ill and nearly all moderately ill patients had dehydration and toxemia In nine patients arthritis suggestive of severe rheumatic fever developed after the acute stage with diarrhea and fever had subsided—an average of two weeks after onset of illness Arthritic symptoms persisted for several weeks or a month or two

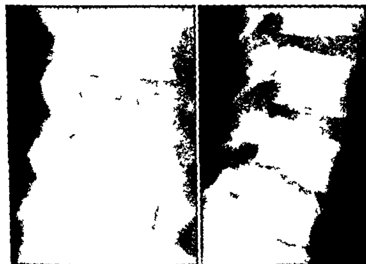
The organism could not be demonstrated in fecal specimens in 47% of the patients Of the 287 in whom S typhimurium was found in the stools 89% showed a positive Gruber Widal reaction

Clinical symptoms were unaffected whether or not anti

(7) Acta m. d. scand av 153 1 20 1955

biotics were given and antibiotics did not hasten freedom from bacilli In repeated in vitro tests S typhimurium bacilli were sensitive to the three broad spectrum antibiotics used Doses of antibiotics were comparatively small and results might have been different if larger doses had been given for longer periods However the ineffectiveness of antibiotic therapy demonstrated in the study suggests that broad spectrum antibiotics are useless in general practice for treatment of S typhimurium infection

Osteomyelitis of Spine Due to Salmonella Cholerae Suis is reported by Edgar L Ralston[8] (Univ of Pennsylvania)



F g 1 (l ft) —X y fou w k aft h p tal zat on rt bral d tru tion t m gi of d sk betw en 4th a d 5th l mba rtebra de e f xten bsc s f rm t on
F g. 2 (r ght) —X y bout 10 month ft onset f llne rt bral d tru t on m r prono d, llaps f d k
(Courtesy f Ralston E L J Bon & J int S g 37 A 590 594 Jun 1955)

Involvement of the spine has not been recorded previously although osteomyelitis has been Harvey in 1937 reported 71 cases of infection due to S cholerae suis with bone and joint involvement in 15 Multiple skeletal involvement was reported in all fatal cases

(8) J Bone & Jo t Su g 37 A 580 584 J 19

suggests that other food products similarly processed should be closely scrutinized bacteriologically

Epidemic Due to Salmonella Typhimurium (Breslau) Occurring in Sweden in 1953 With Special Reference to Clinical Complications Bacteriology Serology Antibiotic Treatment and Morbid Anatomy The epidemic arose from meat contaminated by S typhimurium in a slaughterhouse There were 8 569 cases reported between June 15 and Dec 31 1953 In Stockholm about 900 patients were hospitalized and 654 of these with infection verified bacteriologically or serologically were studied by Elias Bengtsson Per Hedlund Åke Nisell and Hans Nordenstam[7] Of the 309 males and 345 females 136 were under age 15 and 44 over age 65

Of the 654 cases 43 were severe and 156 moderate the other 75% being mild Of children under 15 only 2 were severely affected in old people the reverse was true and of 16 aged patients gravely ill 7 died On the average duration was one week for mild and two for moderate or severe cases

Predominant clinical symptoms were fever diarrhea and vomiting Nearly all patients had violent diarrhea usually lasting four to six days and in 138 persisting for one to two weeks The white blood cell count was usually normal but in 12% was less than 4 000/cu mm

Complications included thrombosis thrombophlebitis and cystopyelitis in 18 patients and pneumonia in 6 Blood cultures were positive in only 5 of 159 patients Osteomyelitis in one of the cuneiform bones was seen only once in a woman aged 28 All severely ill and nearly all moderately ill patients had dehydration and toxemia In nine patients arthritis suggestive of severe rheumatic fever developed after the acute stage with diarrhea and fever had subsided—an average of two weeks after onset of illness Arthritic symptoms persisted for several weeks or a month or two

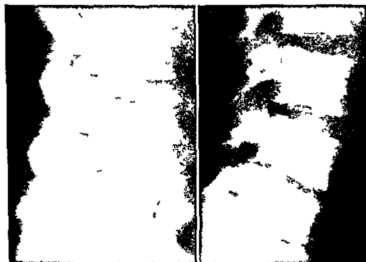
The organism could not be demonstrated in fecal specimens in 47% of the patients Of the 287 in whom S typhimurium was found in the stools 89% showed a positive Gruber Widal reaction

Clinical symptoms were unaffected whether or not anti

(7) Acta med scand nav 153 1 20 1955

biotics were given and antibiotics did not hasten freedom from bacilli In repeated in vitro tests S typhimurium bacilli were sensitive to the three broad spectrum antibiotics used Doses of antibiotics were comparatively small and results might have been different if larger doses had been given for longer periods However the ineffectiveness of antibiotic therapy demonstrated in the study suggests that broad spectrum antibiotics are useless in general practice for treatment of S typhimurium infection

Osteomyelitis of Spine Due to Salmonella Cholerae Suis is reported by Edgar L Ralston[8] (Univ of Pennsylvania)



Fg 1 (l ft) —X y f w k ft h p t l t on t b l d tru t on t m g f d k b tw n 4th d 5th l mb rt bra n den of xt bsc f m t

Fg 2 (ght) —X y b t 10 m th ft r on t f ll rt bral d tru t mo pron d ll p f d k

(Court y f Ral t E L J B & J t S g 37 A 580 584 J 1955)

Involvement of the spine has not been recorded previously although osteomyelitis has been Harvey in 1937 reported 71 cases of infection due to S cholerae suis with bone and joint involvement in 15 Multiple skeletal involvement was reported in all fatal cases

(8) J B e & Jo t S g 37 A 580 584 J 1955

Man 28 had acute low back pain on the right side beginning three days before hospitalization Temperature was 102 F pulse 72 and respiration and blood pressure normal The lungs were clear there was no tenderness over the abdomen and no masses were palpable There was a point of acute tenderness along the right iliac crest just lateral to the posterior superior spine but no mass or fluctuation The spinous processes were not tender and deep fist percussion of the spine elicited no tenderness

The white blood cell count ranged between 5 000 and 6 000 Blood cultures grew S cholerae suis No organisms of the salmonella group were recovered from the stool or urine Figure 1 illustrates the repeat roentgenograms of the lumbar spine showing destruction of the inferior border of the 4th and the superior border of the 5th vertebra with some loss of disk space

Chloramphenicol was started 2 Gm every six hours One week later temperature began decreasing although pain continued unabated A plaster jacket incorporating both thighs was applied and symptomatic improvement was almost immediate Temperature slowly fell to normal Chloramphenicol was continued for 24 days For several days after it was discontinued temperature rose but returned to normal spontaneously

Ten months later he had no symptoms referable to the spine although vertebral destruction was more pronounced and the disk was collapsed (Fig 2)

• [S cholerae suis is notorious for the variety of its systemic manifestations —Ed]

Isolation of Salmonella Typhi from the Blood Stream the most definitive diagnostic measure in early stages of typhoid fever was studied by Kenneth C Watson[9] (Pietermaritzburg Union of South Africa) Bacteremia is present in the first few days of the illness while isolation of the organism from stools or urine is of no help at this time and serologic procedures are not yet definite

METHOD —Blood was cultured by adding 8-10 ml whole blood from venipuncture to 35 ml of 0 5% taurocholate broth in 4 oz screw capped sterile bottles Clots were cultured by removing the serum from 5 ml volumes of clotted blood collected in sterile 3× ⁄ in tubes The residual clot was added to 15 ml streptokinase bile salt broth (containing 100 units of streptokinase/ml) in universal containers Streptokinase produced rapid clot lysis with release of the organisms from the clot

Simultaneous cultures of whole blood and clot were done in 104 patients Blood cultures were positive in 52 and negative in 52 clot cultures were positive in 98 patients and negative in only 6 The clot technic obviously superior suggested that presence of serum in sufficient concentration ad

(9) J Lab & Cl M d. 46 128 134 July 1955

versely affected percentage of positive cultures With a blood medium ratio of more than 1/4 1/5 chances of a positive culture are diminished

A number of factors are important The volume of medium must be sufficient to dilute out any bactericidal serum factors that may be present in the whole blood culture A large volume of blood is necessary because the average case of typhoid fever has a low degree of bacteremia Previous vaccination with T A B apparently has little effect in influencing successful isolation Even if the patient is afebrile and often despite administration of chloramphenicol positive blood cultures may be obtained

• [Clot culture sometimes works well with brucella too This is probably not of much importance with many kinds of bacteremia since the growth of many pathogens is not so adversely affected by antibody —Ed]

Surgical Treatment of the Chronic Typhoid Carrier Report of 102 Operated Cases is presented by W Anders F Linder and W Stephan[1] (Berlin) The cholecystectomies performed in chronic typhoid and paratyphoid carriers *were successful in 90% of the patients* i e *absence of typhoid or paratyphoid bacilli in feces on regular bacteriologic examination for at least a year* To achieve such satisfactory results the following indications for operation must be strictly observed (1) Bacilli must be excreted in feces only with urinary findings negative (2) The gallbladder must be abnormal either nonfunctioning or containing gallstones (3) There must be no acute gallbladder disease In nearly all gallbladders removed stones or evidence of inflammation was noted Gallbladder carcinoma was found in one Results are especially good because the operation carries only a small risk other methods of abolishing the carrier state have not proved satisfactory and reliable and usually a diseased gallbladder is removed

• [Surgery continues to be the method most likely to eradicate the typhoid carrier state —Ed]

DIARRHEAL INFECTIONS

Acute Diarrheal Diseases of Bacterial Origin are reviewed by Francis S Cheever (Univ of Pittsburgh) The distinc

(1) D tsch m d W h sch 80 1637 1641 N 11 1955
( ) B ll N w Y k A ad M d 31 611 6 6 S pt mbe 1955

Man 28 had acute low back pain on the right side beginning three days before hospitalization Temperature was 102 F pulse 72 and respiration and blood pressure normal The lungs were clear there was no tenderness over the abdomen and no masses were palpable There was a point of acute tenderness along the right iliac crest just lateral to the posterior superior spine but no mass or fluctuation The spinous processes were not tender and deep fist percussion of the spine elicited no tenderness

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(9) J Lab & Clin M d 46 128 1 4 July 1955

during therapy with broad spectrum antibiotics is presumably an infection rather than an intoxication

So called food poisoning caused by salmonella salmonella gastroenteritis is an important cause of diarrhea Salmonella typhimurium is reportedly isolated from 30 40% of all outbreaks in the United States and Canada These organisms are parasites of lower animals and man frequently is infected by ingesting tissue (meat poultry) or eggs and dairy products from infected animals Since the incubation period is 12 24 hours the process is probably a bacterial infection in which the organisms multiply in the gastrointestinal tract to reach a critical number Cramping abdominal pain diarrhea and headache then begin abruptly Nausea and vomiting are rarely severe or protracted Fever is nearly always present The stools foul smelling at first and then becoming liquid have an inflammatory exudate on microscopic study

Diagnosis of salmonella food infection requires that salmonella be isolated from the suspected food The relatively longer incubation period fever and constitutional symptoms and absence of excessive vomiting differentiate it from staphylococcic enterotoxic gastroenteritis

[A good statement of the high lights of differential diagnosis —Ed]

Studies on Ameba Bacteria Relationship in Amebiasis Comparative Results of Intracecal Inoculation of Germ free Monocontaminated and Conventional Guinea Pigs with Endamoeba Histolytica are reported by Bruce P Phillips Patricia A Wolfe Charles W Rees Helmut A Gordon Willard H Wright and James A Reyniers[3] (Univ of Notre Dame)

Symbiosis of associated micro organisms in the etiology of disease is largely unknown although each of many organisms is responsible for a specific disease syndrome The normal flora of animal hosts may influence infectivity and/or pathogenicity of many micro organisms Such a relation ship is possible with E histolytica the causative organism of amebiasis

Endamoeba histolytica derived from cultures of the ameba with Trypanosoma cruzi was inoculated into germ free monocontaminated and conventional guinea pigs to ascertain

(3) Am J T p M d 4 675 692 J ly 1955

tion between diarrhea and dysentery is clinicopathologic rather than etiologic *Frequent bowel movements are called* diarrhea when blood pus or mucus is present the term dysentery is used Salmonella and strains of staphylococcus may cause acute gastroenteritis commonly called food poisoning since contaminated food is the usual vehicle

Bacillary dysentery is an infection chiefly of the colon and less often of the distal ileum In the United States the more important etiologic agents are Shigella sonnei and flexneri Average incubation period is 48 hours and severity varies from *slight diarrhea* to prostrating dysentery *Abdominal* cramps occur first followed by diarrhea and except in mild cases accompanied by pus mucus and frequently blood Fever is common Diagnosis is confirmed in the laboratory Microscopic examination of the stool reveals predominant polymorphonuclear elements Culture should be taken by sigmoidoscope but the rectal swab is the most practical

General supportive measures include bed rest codeine or morphine fluids and electrolytes as needed and antimicrobial therapy The *broad spectrum antibiotics are all effective* Sulfonamides have been used the soluble compounds being the most effective

The commonest type bacterial food intoxication causing diarrhea is staphylococcic enterotoxic gastroenteritis Incubation period averages one to four hours nausea and vomiting begin suddenly and diarrhea follows often accompanied *by headache abdominal pain and prostration* Acute *symptoms rarely last more than 6 hours most patients are almost* recovered by 24 hours and the fatality rate is practically nil

The diagnosis depends on sudden onset of typical symptoms among individual members of a group There is no cellular exudate in the stools gross blood is rare and mucus is not conspicuous Significant numbers of staphylococci *should be isolated from suspected foods* There *are no reli*able laboratory tests for detecting the toxins Bed rest is easily enforced during the active phase since the patient is nearly always incapacitated Antispasmodics are not indicated Chemotherapy against the causative cocci is unnecessary since they do not multiply in *the gastrointestinal* tract

The acute staphylococcic gastroenteritis that develops

disease The clinician and not the bacteriologist should make the final interpretation of laboratory findings Jay P Sanford Cutting B Favour Frances H Mao and J Hartwell Harrison[4] reiterate the value of the poured plate technic correlated with the usual procedures in studying urine of persons with infection suspected

TECHNIC—After centrifugation a portion of urine sediment was removed by sterile loop placed on a slide and stained with methylene blue and a loopful was streaked onto a blood agar or an eosin methylene blue agar plate and/or onto a blood agar plate containing 0 07% sodium azide A loopful of sediment was inoculated into thioglycolate broth Single colony isolations were made after 24 hours incubation at 37 C An uncentrifuged portion of urine the amount depending on the number of bacteria seen in the sediment was then used to prepare a pour plate If no or rare organisms were seen 1 ml undiluted urine was used If the sediment was loaded with bacteria 0 1 ml original urine was diluted with 9 9 ml sterile distilled water and 0 1 ml of this dilution (0 001 ml original urine) was used Into a sterile Petri dish 1 ml was pipetted and 9 ml melted cooled tryptic digest agar was added and mixed by swirling

From 164 patients with clinical symptoms or signs of urogenital infection 250 separate consecutive cultures of urine were studied In 15 6% of the cultures no bacteria grew mixed bacterial flora was cultured in 16 8% With 1 000 colonies/ml as the dividing point (not an absolute value but an order of magnitude) 55 of the 190 cultures counted had less than this total apparently insignificant numbers of bacteria

Correlation between bacterial counts and microscopic examination of the centrifuged urinary sediment revealed that absence of pyuria in single or multiple urine specimens did not negate diagnosis of urinary tract infection Leukocytes were not demonstrable in 13 of 91 specimens with large numbers of bacteria (more than 10 000/ml) Neither did presence of pyuria always imply that a pyogenic urinary tract infection was present About 5 000 10 000 viable organisms/ml had to be present before they could be seen on stained smears of centrifuged sediment

The studies showed that presence of a moderate number of bacteria on a stained smear is highly suggestive of significant bacteriuria Pyuria during infection is variable and not closely correlated with clinically significant bacteriuria

• [This problem seems to me to be one of great practical significance

(4) Am J Med 20 88 93 January 1956

the role of the intestinal flora in the cause pathogenesis and pathology of amebiasis

Results in the conventional (control) guinea pigs were in contrast to those in the germ free animals Of 37 controls 34 developed acute ulcerative amebiasis The other three were found to harbor the ameba when killed on the 21st day Of the animals with amebic ulcers 14 died of the disease 6 20 days after inoculation and the other 20 had amebic ulcers when killed

None of 35 germ free animals that received inoculums identical with those of the controls developed amebiasi They were killed at intervals of 1 to 33 days

Inoculation into monocontaminated animals provided additional information Endamoeba histolytica introduced into animals harboring either Escherichia coli or Aerobacter aerogenes as monocontaminants caused acute amebiasis Either or both of these bacteria seemed of potential significance in the etiology of amebiasis At present it is impossible to ascertain to what degree either the ameba or the intestinal flora participate in causing the disease Bacteria may be a major factor

Endamoeba histolytica is unquestionably the causative organism of intestinal amebiasis but the responsibility for the disease must be shared with other organisms which contribute to the etiology pathogenesis and pathologic condition In absence of microbial associates ameba appeared harmless microbes incapable of independent survival in the intestine

• [An excellent application of Reymers elaborate technic for rearing laboratory animals in a germ free environment —Ed.]

URINARY TRACT INFECTIONS

Evaluation of 'Positive' Urine Culture Approach to Differentiation of Significant Bacteria from Contaminants A positive culture on a urine specimen apparently collected aseptically may mean clinically significant infection in the urinary tract or the structures draining into it or it may be due to contamination during collection or handling of the specimen and thus not associated with significant clinical

Without change in position of the patient 8 × 10 in roentgenograms are made in posteroanterior and lateral projections immediately processed and studied Further adjustments of the needle and additional films are made as necessary Aspiration is done and the material cultured and studied microscopically

Prognosis of this type osteomyelitis is in general favorable as the healing tendency is pronounced Extensive destructive changes are rare and complete disintegration of one or several vertebrae common in tuberculosis is not to be expected

• [Apparently urologists and orthopedists are aware of this complication but it is not well known generally —Ed]

BACTEREMIA DUE TO ENTERIC ORGANISMS

Bacteremia Owing to Gram Negative Bacilli Experiences in Treatment of 137 Patients in a 15 Year Period are reported by John A Spittel Jr William J Martin and Donald R Nichols[6] (Mayo Clinic and Found) *Only patients from whom two or more positive blood cultures were obtained and in whom clinical examination indicated obvious bacteremia were included in the study* So called transient bacteremia occurring after urologic or dental instrumentation in which bacterial invasion of the blood stream is fleeting was not included nor was typhoid brucellosis or bacterial endocarditis

The commonest gram negative bacillus to invade the blood stream is Escherichia coli In about 60% of the patients the genitourinary tract was the portal of entry and in about 25% the gastrointestinal tract including the biliary passages

Treatment consists of 1 Gm streptomycin intramuscularly every 12 hours and tetracycline 0 75 Gm orally every 6 hours Probably these two drugs combined have a synergistic effect against bacteremia due to gram negative bacilli (except Pseudomonas aeruginosa) Treatment is continued until three successive blood cultures are negative and the patient is afebrile for 72 hours Since the infections usually subside within two weeks there is little danger of toxicity from streptomycin in such amounts when renal function is normal All the tetracycline preparations are equally effective

(6) A I t M d 44 30 314 F t ry 1956

Catheterization to obtain a specimen for culture is not absolutely reliable since the bladder urine may be contaminated by organisms from the urethral canal furthermore catheterization may be the means of infecting a previously noninfected urinary tract These workers by using a quantitative technic and solid mediums have a method in which nonsignificant contaminants can usually be recognized. It is analogous to bacteriologic examination of other contaminated areas—throat nose sputum open wounds —Ed.]

Spinal Osteomyelitis Associated with Urinary Tract Infections Ted F Leigh Robert P Kelly and H Stephen Weens (Emory Univ) report on nine patients with spinal osteomyelitis following one or more bouts of urinary tract infection Batson has demonstrated broad communications between the venous plexus of the pelvic organs and that enclosing the spinal cord and surrounding the spinal column The vertebral plexus a network of valveless blood vessels has numerous communications with the veins of the body cavities at various intervertebral levels

Deviation of the venous blood stream into the vertebral channels may occur in such maneuvers as straining coughing sneezing and perhaps even abdominal distention The bizarre spread of carcinoma of the prostate could be explained by the general distribution of this venous plexus Similarly spread of paradoxical metastases and propagation of inflammation may be attributed to a preferential blood flow through the vertebral venous pathways

Gram negative bacilli are important in causing spinal osteomyelitis after urinary tract infection and instrumentation Organisms were recovered from the vertebral abscesses in four of these patients pseudomonas in one Proteus vulgaris in one Escherichia coli in one and Staphylococcus aureus in one Roentgen evidence of a lesion in the spine lags behind clinical manifestations by weeks or months Initial films soon after onset of back pain frequently show no abnormalities then additional studies should be made every few weeks For proper therapy the causative organism must be exactly identified which is best accomplished by aspiration under roentgenographic guidance

TECHNIC—To recover the organism the patient is anesthetized and placed prone on the radiographic table The area on the back near the lesion is cleansed and draped and the skin punctured with a Biers 15 gauge 3½ in stainless steel spinal needle directed anteriorly and obliquely inward toward the lesion in the vertebral bodies and disk

(5) Radiology 65 334 September, 1955

tions subsided leukocytes decreased and thrombocytes increa ed to 290 000 and 300 000/cu mm

During convalescence a calculus was removed from the left ureter Late during hospitalization the serum agglutinated in dilutions up to 1 1200 the strain of P vulgaris isolated from the urine She was discharged as cured 26 days after admission

• [It is fortunate that this strain of proteus was sensitive to chloramphenicol too often none of the commonly used antibiotics is effective against proteus —Ed]

Shock Associated with Bacteremia Review of 35 Cases is presented by Wendell H Hall and David Gold[8] (V A Hosp Minneapolis) Hypotension is frequent in typhoid fever peritonitis cholera bacillary dysentery gas gangrene diphtheria meningococcemia and several rickettsial diseases Prostration dehydration fever cardiac failure and adrenal insufficiency have been postulated but the precise mechanism is unclear Hypotension often is unrecognized because of signs and symptoms of bacteremia The patient often is alert and at first may have suffused warm dry skin One must be alert to detect hypotension during infection and infection may be overlooked in a patient in shock

During seven years 35 patients most over age 45 had shock associated with bacteremia Of the 35 18 died the mortality rate being 51% The most frequent underlying disease was malignant neoplasm and 7 of 11 patients with malignant disease died shortly after an episode of bacteremia and shock

The source of bacteremia leading to shock was most frequently the genitourinary tract The bacteria isolated from the blood were paracolobactrum proteus Micrococcus pyogenes var aureus Escherichia coli Aerobacter aerogenes Diplococcus pneumoniae Streptococcus pyogenes Klebsiella pneumoniae and Neisseria catarrhalis Gram positive cocci were responsible in 34% and gram negative bacilli in 66% of the episodes of shock

Bacteremia began abruptly in nearly all patients and was marked by a shaking chill After the chill and before the fall in blood pressure body temperature rose abruptly in 32 patients

Shock as ociated with meningococcic infections (Waterhouse Friderichsen syndrome) has been attributed to hem

(8) A M A A h I t M d 96 403 412 Sept mbe 1955

Treatment is initiated empirically when blood cultures are reported positive If in vitro inhibition tests indicate that another antibiotic would be more effective the program is re evaluated If the patient seems to be improving on the original program the regimen is not changed merely be cause so called sensitivity tests indicate selection of another agent

Polymyxin B sulfate must be used with utmost caution It has been used only in infections due to Ps aeruginosa and in retractory cases of Aerobacter aerogenes bacteremia Fre quently pain at the site of injection is severe As with strep tomycin and dihydrostreptomycin acral and circumoral par esthesia may occur but is more severe with polymyxin Other reactions include cerebellar ataxia and renal damage The recommended daily amount of the drug for adults is 100 200 mg intramuscularly in four doses

Blood Stream Infection Due to Proteus Vulgaris and Causing Thrombocytopenic Purpura Recovery with Use of Chloramphenicol is reported in one case by Max H Stein and Elias Gechman[7] *(Brooklyn)* Purpura was recognized as a manifestation of pestilential fevers 2 000 years ago Since then it has been observed in many infectious states such as septicemia typhoid fever typhus relapsing fever tubercu losis smallpox chickenpox vaccinia scarlet fever measles rubella and subacute bacterial endocarditis

Woman 47 had chills and fever for two days and lumbar pain *for* five Physical examination revealed bilateral splinter shaped conjunc tival hemorrhages and generalized purpuric spots with bleeding from the buccal mucosa and tarry stools Temperature of septic type ranged from *99* to *104* F the first five days after hospitalization and hemorrhagic manifestations persisted Urinalysis showed 1 12 white blood cells per high power field Repeated urine cultures grew P vul garis and blood cultures on the day of and day after admission re sulted in a heavy growth of the same organism extremely sensitive to chloramphenicol Platelet counts on the first four days of hospitali zation were 30 000 20 000 and 20 000/cu mm blood

Before the organism was identified she was empirically started on combined antibiotics — 40 000 000 units of penicillin 4 Gm strep tomycin and 4 500 mg oxytetracycline — without favorable response When the organism was identified as P vulgaris sensitive to chlor amphenicol this drug was started 750 mg being given every four hours by mouth all other antibiotics were discontinued Within two days the toxic condition improved fever and hemorrhagic manifesta

(7) New England J Med 25 906 908 May 26 1955

to prevent or correct the severe plasma volume deficiency was given to four dogs but did not ameliorate basic disturbance. Course of the shock state did not differ from that in untreated dogs and death ensued.

Prophylactic antibiotic therapy without fluid volume therapy in 10 dogs did not prevent severe hypovolemia or other hemodynamic disturbances but death was prevented in 9. Cultures of the peritoneal fluid were never sterile but usually the number of bacteria seen on smear decreased after the sixth hour. The number of leukocytes seemed to be larger and the degree of phagocytosis was greater than in the other dogs.

The fall in circulating blood volume was largely due to the peritoneal exudate and to a small extent to losses by vomiting, diarrhea and insensible fluid loss.

In septic, as in hemorrhagic, shock the hemodynamic disturbances of hypovolemia are not per se necessarily lethal. They can be much better tolerated if bacterial activity can be suppressed before a lethal amount of toxin has been produced.

• [This is one of a series of studies by Fine and his associates who seem convinced that bacterial endotoxins play a significant role in the circulatory failure of infection and that the possibility of complicating infection must be considered in shock due to other causes such as hemorrhage.—Ed.]

SUBACUTE BACTERIAL ENDOCARDITIS

Successful Short Term Therapy of Streptococcic Endocarditis with Penicillin and Streptomycin. Buford Hall, Harry F. Dowling and William Kellow[1] (Univ. of Illinois) treated 15 patients with endocarditis caused by penicillin sensitive alpha and gamma streptococci with short term therapy. Most authorities advocate four to eight weeks of treatment when penicillin alone is used but after in vitro experiments with penicillin and streptomycin this combined therapy was proposed for penicillin sensitive streptococci. Hunter successfully treated five patients with a 10 day course of 2,500,000 units of penicillin and 2 Gm. streptomycin daily.

A regimen of four to six weeks of therapy for subacute endocarditis has many disadvantages. Besides discomfort of

(1) Am J M S 30 73 81 J ly 19 5

orrhage in the adrenal glands and subsequent adrenal insufficiency Autopsy in 14 of the 18 patients who died revealed hemorrhage and necrosis in the adrenals of only 1 Adrenal insufficiency has not been proved to play a frequent role in any form of bacteremic shock

No ideal program for treating bacterial shock is available Early and effective antibacterial therapy is essential Cortisone and ACTH with antibiotics have been reported helpful in severe infections with suppression of fever neutrophilic leukocytosis and other toxic signs Four patients were given these steroids or adrenocortical extract but only one recovered

A moderate amount of whole blood pooled plasma or other plasma volume expander may be helpful Despite physiologic vasoconstriction in the skin of the extremities blood pools in the periphery Vasoconstrictor drugs have been extensively used Levarterenol is the most effective and was given to seven patients In relatively large doses continuously it produced sustained elevation of blood pressure In a few patients urinary output was low during levarterenol therapy despite adequate blood pressure This may have been due to excessive renal vasoconstriction

• [The points that infection may be an occult cause of shock and that patients with infection may have marked hypotension and still not present the clinical picture of shock deserve reiteration —Ed]

Effect of Antibiotics on Hemodynamics of Hypovolemic Septic Shock Edward D Frank Dorothy Kaufman Henry Korman Fritz Schweinburg Howard A Frank and Jacob Fine[9] (Boston) induced peritonitis in healthy dogs by injecting dog feces intraperitoneally

The hemodynamic disturbances induced by septic shock were much the same as those of prolonged hemorrhagic shock Plasma volume was reduced by 45% at nine hours hematocrit value increased to about 75% and red cell volume remained within normal limits Oxygen consumption declined steadily arteriovenous oxygen difference increased and cardiac output fell Arterial blood pressure was sustained for a few hours then fell gradually until a few hours before death when it declined precipitously

Fluid volume therapy with plasma in amounts sufficient

(9) Am J Phy ol 18 166 176 J ly 1955

murmur fever and positive blood cultures Average duration of disease before therapy was about 4 months the range being 1½ 12 months

Response to therapy was uniformly good Symptomatic improvement was prompt in most patients Temperature became normal during the first 24 hours in 12 patients during the 2d day in 4 and during the 3d and 4th days in 1 each One patient had temperature persistently elevated for 10 days before it returned to normal Another was afebrile when therapy was started and three others had low grade slightly irregular fever Of the 23 patients 21 were cured and 2 died Another patient died five months after treatment while considered to be in good health Of these three one died of congestive heart failure on the fourth day of treatment one of massive cerebral infarction due to embolus on the ninth day and one of a subarachnoid hemorrhage five months after therapy possibly from a previous cerebral embolus and subsequent mycotic aneurysm Of the 20 who were living none relapsed during follow up of 2 23 months At periodic examination every one or two months all were well and active

Reports by several authors on short term combined therapy revealed three failures in 61 patients Of the 46 patients from the Mayo Clinic none of the living patients had relapsed and treatment had not failed in any

Patients with subacute bacterial endocarditis caused by strains of streptococci of intermediate sensitivity to penicillin (inhibited by 0 1 1 units/cc medium) are apparently as effectively treated by short term combined therapy as are those with infections due to penicillin sensitive organisms (inhibited by 0 1 unit or less)

Cure and survival rates of 100% are not to be expected even in an infection easy to cure when average duration of symptoms before adequate therapy is long Most of the patients had received a few doses of penicillin or the broad spectrum antibiotics for variable lengths of time without a definite diagnosis being made Diagnosis was made within two months of onset in only three patients Earlier diagnosis with prompt adequate combined antibiotic therapy might possibly give a cure rate of 100%

Subacute Bacterial Endocarditis Splenectomy in Cases Refractory to Antibiotic Therapy A few cases have been re

frequent injections over a long period and cost of prolonged hospitalization it is difficult to persuade some patients to undertake such a long course of treatment and the physician sometimes encounters a more subtle opposition in his own mind if there is any doubt about the diagnosis Therefore short term therapy with penicillin and streptomycin which insures results comparable to the conventional method is preferable Mortality rates complications and relapses are no more frequent than with long term treatment Streptomycin toxicity has not been reported in any of the patients

Combined penicillin streptomycin therapy 600 000 units of aqueous procaine penicillin G intramuscularly at 6 hour intervals for 10 days and 0 5 Gm of a mixture of equal parts of streptomycin and dihydrostreptomycin intramuscularly at 6 hour intervals for 5 days and at 12 hour intervals for another 5 days is satisfactory for streptococcic endocarditis in which the organism is sensitive to 0 2 unit of penicillin or less/cc

The authors emphasize that penicillin and streptomycin in these doses are suitable for penicillin sensitive streptococci only Endocarditis caused by penicillin resistant streptococci should be treated with larger doses of penicillin plus streptomycin for a longer time

• [In this and the subsequent article we see a revival of interest in the possibility of cutting down the duration of therapy in subacute bacterial endocarditis in cases where the causative organism is penicillin sensitive This seems rational to me and has worked well in cases I have followed Actually with the advantage of present day dosage schedules of penicillin and the synergistic effect of streptomycin there does not seem to be good basis for insisting on six to eight weeks of treatment in every case It must be stressed however that short courses should be restricted to cases of relatively short duration caused by penicillin sensitive organisms —Ed]

Further Experiences with Short Term (Two Weeks) Combined Penicillin Streptomycin Therapy for Bacterial Endocarditis Caused by Penicillin Sensitive Streptococci A previous report included 23 cases Joseph E Geraci[2] now summarizes experiences with 23 additional patients seen between March 1953 and February 1955

After diagnosis was established treatment was started with 1 000 000 units of aqueous procaine penicillin and 1 Gm combined streptomycin and dihydrostreptomycin intramuscularly every 12 hours for 2 weeks Every patient had a heart

(2) Proc Staff M et Mayo Clin 30 192 00 May 4 1955

weeks or longer Intrathecal administration had no advantage over the intravenous or intramuscular route Antitoxin dosage should be independent of body weight

Penicillin had no effect on tetanus toxin Administration when tetanus bacilli first entered the body did not prevent the clinical disease although antibiotics may be helpful in preventing or ameliorating complicating bacterial infections

General care supportive measures and nursing and medical supervision are important Patients must be protected against aspiration fecal impaction urinary retention bed sores injury from thrashing about traumatic glossitis and undue excitement and stimulation Surgical principles for the treatment of tetanus should be the same as for other conditions Sedation is essential to control repeated convulsions prevent respiratory embarrassment caused by laryngospasm or respiratory muscle rigidity relieve pain and minimize the effects of external stimuli

Complications of tetanus have included vertebral fractures serum sickness and traumatic glossitis Mediastinal emphysema has resulted from tracheotomy

In the 15 patients reported on all procedures were deferred until satisfactory sedation had been achieved Abdominal muscle relaxation in the presence of a cough response to tracheal suction was a desirable goal Thiopental was given by constant intravenous infusion Antitoxin was given after tests for sensitivity shortly after admission one half intravenously and one half intramuscularly or into the area around the wound

Tracheotomy was done in 10 patients Copious quantities of tracheobronchial secretions were aspirated from several patients at the time of tracheotomy Secretions could be aspirated at will effects of laryngospasm were obviated and bronchoscopy could be easily carried out in the five patients who required it After tracheotomy sedation could be decreased in some patients and the danger of aspiration of gastric contents or pharyngeal ecretions was lessened Despite the additional care required patient care was easier after tracheotomy The tracheotomy tube was left in place until large amounts of sedatives were no longer needed and the patient could eat and drink without laryngospasm

All patients were kept in a quiet semidarkened room with

ported in which removal of the spleen the site of an infarct or abscess resulted in *cure of subacute bacterial endocarditis* Recent reports have suggested that the spleen may be responsible for continued bacteremia in this disease Probably more often than suspected a splenic infarct becomes infected The *necrotic material protected* by granulation or fibrous tissue is excellent culture medium for bacteria Antibiotics even in high blood levels apparently cannot penetrate the barrier to eradicate the focus

Carolyn J Lingeman Edward B Smith J S Battersby and Roy H Behnke[3] (Indiana Univ) report on three patients Each had typical subacute bacterial endocarditis severe pain in the *left upper quadrant* of the abdomen and continuous bacteremia in presence of high blood levels of antibiotics Each had evidence of pleural reaction or fluid accumulation in the adjacent left hemithorax After splenectomy each became afebrile and repeated blood cultures were negative The spleens of all three contained infected infarcts and streptococci were cultured from two

• *[This is surely uncommon and the postulate that antibiotics could not penetrate a necrotic infarct is not appealing nevertheless it may be true that in rare instances splenectomy will turn the tide —Ed]*

TETANUS

Management of Tetanus Report of 15 Consecutive Cases with Recovery Gilbert B Forbes and Marian Auld[4] report results in patients treated at the Children s Medical Center Dallas and the Dallas City County Hospital from 1950 to 1953 In a review of selected literature the mortality rate was high although the disease was not common In those who survived recovery was complete The mortality rates reported (20 60%) probably are responsible for the prevailing *semidefeatist attitude Recently the prognosis* has been improving Severity of the disease varies inversely with the incubation period Prognosis seems distinctly unfavorable at the two extremes of life *with little variation between 1* and 50 years of age

A single injection of 30 000 100 000 units of antitoxin provided a satisfactory level of antitoxin in the *blood for five*

(3) A M A Arch Int Med 97 309 314 March 1956
(4) Am J Med 18 947 960 Ju 1955

of the mouth to the left He had a 1 cm deep perforation filled with pus but with little surrounding inflammation just within the hair line above the left eye He had definite facial asymmetry and left sided spasm with a narrowed left palpebral fissure the eyebrow drawn down despite spasm of the frontalis muscle the corner of the mouth drawn to the left and a deepened nasolabial crease (Fig 3) Chvostek s sign was present with spasm of both the orbicularis and perioral muscles

Cultures of excised tissue from the puncture wound grew Clostridium histolyticum Cl tetani a nonhemolytic streptococcus and Micrococcus pyogenes Within two hours of admission treatment was begun with tetanus antitoxin penicillin and streptomycin Three days after admission because of progression of signs and symptoms the wound was excised under local anesthesia He was always able to open his mouth about 1 cm and thus able to eat After 12 days gradual improvement set in Several weeks after discharge the left palpebral fissure was still narrowed

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RICKETTSIAL DISEASES

Incidence of Epidemic Typhus Antibodies in Individuals Born in Eastern Europe Gerschen L Schaefer Murray Friedman and Christeen Lewis[6] (Mount Sinai Hosp Chicago) found epidemic typhus antibodies in 22% of serums of 100 unselected patients aged 50 76 born in eastern Europe None had symptoms or signs of typhus Of 60 persons in the same age group born in the United States or Canada not one had demonstrable antibodies In another study reported from Philadelphia 17% of 69 persons born in eastern Europe showed positive results of complement fixation tests for epidemic typhus antibodies

Though endemic typhus has been reported in many small mammals throughout the United States—and this may be important in dissemination of the disease—findings of these studies suggest the possibility of a human reservoir for the rickettsia Increased awareness of Brill s disease as a clinical entity and high percentage of persons with antibodies for epidemic typhus should lead to caution in diagnosis Criteria for establishing diagnosis of Brill s disease must include demonstration of rise in antibody titer

Important Epidemic of Q Fever (175 Cases) Observed at Batna Algeria which approached in size that of the two

(6) A I t Med 42 979 982 M y 1955

special nurses in attendance constantly Feeding was entirely parenteral and nothing was given by mouth except in two patients only mildly affected Parenteral fluid therapy was carefully supervised and guided by frequent determination of serum electrolytes and nonprotein nitrogen concentrations The wounds were cared for by the surgeons Mephenesin used in only one case was of no value

The survival of all 15 patients may have been fortuitous yet three deaths would have been expected from even the most favorable mortality rate reported in the literature An open airway was of major importance Tracheotomy can be recommended for most patients with severe or moderately severe tetanus

• [This is a good article worth consulting in its complete form I am sure the emphasis on tracheotomy is deserved —Ed]

Local Tetanus Report of a Case Involving Left Facial Muscles is presented by E Converse Peirce II and C Harwell Dabbs[5] (Knoxville Tenn) Tetanus that remains local



Fig 3 —App ra of p t t d f d g (C t f P E C II d D bb C H N w E gl d J Med 3 777 8 N 3 1955)

ized is rare and this case emphasizes the importance of recognizing tetanus early by local signs The clinical picture was striking and early differentiation from intracranial injury probably prevented death

Boy 8 had been struck with a stick on the left side of the scalp two days earlier The family noted periorbital swelling and pulling

(5) New E gl nd J Med 53 777 778 N 3 1955

digestive Infestation apparently was general in the two companies because serologic tests made on the few who did not become ill demonstrated positive agglutination to R burneti at a titer equal to or over 1 320 in two of seven serums

Observations of lack of rhinopharyngitis and strict delimitation of the epidemic to a particular group may in the future be useful in orientation toward diagnosis of Q fever Even observation of pseudogrippal symptoms among troops exposed to conditions conducive to contamination by this rickettsia should arouse suspicion of diagnosis

Prolonged cases with spiking of temperature curves lasting 20 days and severe functional disturbances were characteristic of the epidemic in contrast to the usual brevity and benignity of the disease Intense and prolonged asthenia accompanying Q fever and possibility of long lasting and recurrent types justify early treatment with antibiotics when diagnosis is suspected

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POLIOMYELITIS

Evaluation of 1954 Field Trial of Poliomyelitis Vaccine Synopsis of Summary Report is made by Thomas Francis Jr and Robert F Korns[8] (Univ of Michigan) A placebo control study allowed strict comparison with the test subjects The total of children participating in placebo control areas was 749 236 In these areas 200 745 children (26 8%) received three injections of vaccine and 201 229 (26 9%) received *three injections of placebo* which was *identical* except for no poliomyelitis virus or monkey protein

In the observed control areas the study population totalled 1 080 680 children in the first three grades The second grade children numbering 221 998 (20 5% of the total) received three doses of vaccine The first and third grade children were observed and served as controls

Safety of the vaccine was assessed through specific studies of the cause and extent of absenteeism from school following inoculation in Pittsburgh and Schenectady N Y No significant reactions were observed and the experience was

(8) Am J M S 2 9 603 61 Ju 1955

largest epidemics so far reported—one in Greece among German troops with over 1 000 cases the other in Italy and Corsica in 1945 among allied troops (400 cases)—is reported by M Pierrou G Mimoune and G Vastel[7]

Clinical symptoms are of several types pseudogrippal pulmonary and exanthematous (recently described by Le Gac and Giroud) In cases resembling grippe as in this epidemic diagnosis is difficult because specific clinical signs are absent and symptoms usually mild Presence of Q fever is rarely suspected in sporadic cases and from the practical standpoint it can be studied only during an epidemic Original diagnosis of grippe in this epidemic had to be discarded definitely because of negative Hirst reactions but before that two facts argued strongly against this diagnosis i e *no clinical signs of rhinopharyngeal inflammation were* noted and the epidemic was confined exclusively to two single units in the midst of an overcrowded military establishment with constant intermingling of personnel this led to an epidemiologic investigation

The outbreak lasted from March 24 to the first week of June 1955 Day to day incidence occurred in two waves of five weeks each with the first and more severe cases numbering 165 The last 10 cases also lasted five weeks but were much less severe That the disease affected only members of *two companies of a battalion of parachutists* who had arrived in North Africa some months previously was striking The affected troops had made a long trip in a freight car which had been poorly cleared of straw and manure after recent transport of horses and sheep 10 days before appearance of the first case After arrival in Batna the battalion was billeted in large stables converted into barracks The regiment which usually *lodged there had some horses and a* few sheep but serums from these animals were negative for Rickettsia burneti Serums of convalescents eventually proved that the disease was Q fever Infestation of these patients was massive apparently conditioned by prolonged contact during *the trip in the filthy car* containing dust from animal excreta full of rickettsias Prolonged exposure probably *permitted massive absorption of the pathogen by all* the usual routes of entry—respiratory cutaneomucous and

(7) P es méd 64 4 1 473 M 14 1956

tacts of vaccinated children In each case investigation failed to substantiate the rumor

Among the 137 968 children who received one dose of vaccine there were 130 cases an attack rate of 94 5/100 000 15 cases were noted among the 22 673 who received two or more doses a rate of 66 4 Among the 278 532 unvaccinated children there were 553 cases an attack rate of 198.2/100 000

Effectiveness of the vaccine for all cases was 53% For paralytic cases only effectiveness was 60% These figures parallel those of Francis and associates for protection against type I poliomyelitis

Behavior of Chimpanzee Avirulent Poliomyelitis Viruses in Experimentally Infected Human Volunteers Albert B Sabin[1] (Univ of Cincinnati) points out that poliomyelitis is generally more severe in adults than in very young children Any method of immunization must avoid creating a large adult population without resistance to paralytic poliomyelitis Natural inapparent infection in early childhood provides life long immunity in most of the world population Observations of Paul *et al* (1951) on Eskimos indicated that specific antibodies to the virus were demonstrable 40 years after exposure even in the absence of reinfection Natural infection with poliomyelitis viruses seems to provide a built in booster mechanism

In 1953 Sabin and his co workers segregated from highly virulent strains of each of the immunologic types of poliomyelitis virus variants which are avirulent for monkeys by intracerebral oral and parenteral routes When fed to chimpanzees they produced clinically inapparent immunogenic alimentary infections but not the viremia so commonly found with virulent strains When inoculated into the gray matter of the spinal cord of chimpanzees they were avirulent

In the present study Sabin administered these strains to 30 human volunteers aged 21 30 No antibodies were demonstrated against the viruses Type I II or III virus was given to 26 men in doses of 0 001 1 cc in a teaspoonful of milk The other four received type III virus intramuscularly

With oral ingestion no virus multiplication was demon

(1) Am J M Sc 230 1 8 J ly 1955

identical in both control and vaccinated subjects The vaccine was not implicated as a significant cause of untoward reactions

Blood samples were collected from 40 881 children before vaccination two weeks after the third clinic and again five months later *In general* the response to type I poliomyelitis virus was inferior to response to types II and III

No significant difference was detected in the rates of occurrence of nonparalytic disease in test and control groups When these cases were eliminated and only paralytic cases considered an estimate of 75% effectiveness was obtained in the placebo areas and 62% in the observed areas

The most striking effect occurred in bulbospinal disease in which the vaccine was estimated as 94% effective in the placebo control areas with a lower limit of 81% For spinal paralytic polio the effect was less striking 60% with a lower limit of 39% In observed control areas these differences were even less pronounced but still highly significant

Vaccination was estimated as 80 90% effective against disease caused by type I virus and 90% or more effective against that caused by viruses of types II and III The estimate would be more secure had a larger number of cases been available

Evaluation of Poliomyelitis Vaccination in Massachusetts is presented by Alton S Pope Roy F Feemster David E Rosengard Florence R B Hopkins Boris Vanadzin and Edgar W Pattison[9] (Boston) Massachusetts had its largest epidemic of poliomyelitis just before poliomyelitis vaccine became available in sufficient quantities to protect the whole of the younger population This furnished an unprecedented opportunity to evaluate effectiveness of the vaccine in an epidemic situation

No convincing evidence is available that the epidemic was set off by live virus in the Salk vaccine If the vaccine had started the epidemic there should have been multiple foci with simultaneous outbreaks all over the state Actually the epidemic started in Boston and spread in a wave in all directions but in greater intensity toward the south The vaccine did not initiate the disease in Boston Suggestions were made that there were an undue number of cases in household con

(9) New England J Med 254 110 117 Jan 19 1956

in June and a second sample in November after the close of the poliomyelitis outbreak No virus isolation was attempted from the hospital personnel at this time

Though 31 of the 50 persons working on the acute polio myelitis service had minor illnesses no significant rise in neutralizing antibody titer against any type poliomyelitis virus was present No serologic evidence of infection was found in presumably susceptible hospital personnel who worked in close contact with patients during the acute stages of types I and III poliomyelitis infection This is compatible with clinical experience in hospital personnel but at variance with apparent ease of transmission in family groups and from contact data in the community at large Inapparent infection approaches 90% among sibling contacts of cases in families and secondary clinical attack rate is 2 5% or more

Lack of transmission of infection under hospital conditions is believed to be primarily due to decrease in infectiousness of the hospitalized case This may be related to reduced frequency (and possibly titer) of virus in the pharynx at hospitalization Better sanitation in the hospital may interfere with contact and droplet mechanisms of upper respiratory transmission and with fecal spread of virus

The usual hospital isolation technics appear adequate to prevent transmission of virus from the patient to susceptible personnel under conditions of hospital exposure

• [These results are reassuring and ought to be given a good deal of publicity since there is still much resistance to bring ng patient w th polio myelitis into general hospitals and we sometimes find it difficult to persuade nurses to special cases of poliomyelitis —Ed]

Poliomyelitis in Pregnancy Twenty Year Report from Los Angeles County California Paula Horn[3] (Univ of Southern California) reports on 325 pregnancies among 16 268 patients with poliomyelitis in the period 1934-53 The mortality rate was 5 2%

The severity of the disease and mortality were the same in pregnant and nonpregnant women regardless of pregnancy or trimester of pregnancy Therapy was more difficult during pregnancy especially during the third trimester Protein electrolyte and fluid balance had to be observed and maintained carefully Respiratory obstruction infection and the threat of toxemia were ever present problems

After a patient had become stabilized to respirator care

(3) Ob t & Gyn 6 121 137 A gu t 1955

strated in the mouth or anterior portion of the tongue With the larger doses the viruses multiplied in the throat and lower alimentary tract With the smaller doses no virus was found in the throat even when it was continually excreted in the feces for four to six weeks The smallest amount 0 001 cc containing approximately 10 000 tissue culture doses of virus initiated an immunogenic alimentary infection in all volunteers No viremia was found in any of them and none had a minor illness Amounts of type III virus which readily produced infection after ingestion did not do so after intra muscular injection except in one volunteer in whom the virus localized in the lower intestinal tract The antibody response was variable but was higher in the men with ex tensive viral multiplication in the throat No harmful mu tants were found after multiplication in the alimentary tract

Similar studies are in progress with naturally occurring intracerebrally avirulent types I II and III poliomyelitis viruses recovered from healthy children who had no contact with clinical poliomyelitis Studies on immunization of larg er numbers of human beings are being postponed until com parative studies have indicated the best attenuated strains to use

• [Despite the present wide adoption of the Salk vaccine Sabin and others continue to work toward the development of a safe live virus vaccine assuming that it will provide a longer lasting immunity Certainly it is true that if the effect of the Salk vaccine were only to postpone suscepti bility to adult life the consequences might be most unfortunate The prin cipal hazards in use of live virus for immunization are the possibilities of reversion to a more virulent form and of secondary infection from excre tion of virus by vaccinated subjects —Ed]

Risk of Poliomyelitis Infection among Exposed Hospital Personnel a cause of considerable concern for many years was studied by Paul F Wehrle[2] (Johns Hopkins Univ) in volunteers from personnel of the Baltimore City Hospitals where most cases of acute paralytic poliomyelitis from cen tral and northern Maryland are handled During 1954 128 patients with poliomyelitis 63% with demonstrable paraly sis were hospitalized The study was made to determine ex tent of inapparent infection with poliomyelitis virus among hospital personnel during the season of most frequent oc currence and whether work on acute poliomyelitis wards or exposure to hospital environment increased risk of infection

Initial blood samples were collected from the volunteers

(2) Pediatrics 17 237 245 F bruary 1956

ogenes var aureus enterococci Aerobacter aerogenes Escherichia coli Pseudomonas aeruginosa and species of proteus

The infections were caused by bacteria other than the usual pulmonary pathogens The most likely explanation is that antibiotic therapy inhibited the common pathogens except staphylococci and that the more saprophytic species therefore became predominant Since the opportunity for invasion was ideal they invaded the tissues in certain patients

• [Note the bacteriology here One could have assumed with confidence that the patients were on prophylactic antibiotic therapy when these infections developed This fits nicely with Weinstein s findings (This YEAR BOOK pp 19 and 20)—Ed]

HERPES ZOSTER

Generalized Herpes Zoster Initiating Minor Epidemic of Chickenpox Herpes zoster and varicella have a peculiar relation Numerous cases of varicella have arisen from contact with cases of herpes zoster though the reverse is unusual Experimental inoculation studies in man and animals emphasize the identity of the viruses Immunologic studies demonstrate a definite similarity between them but antigenic identity has not been definitely proved Morphologically the vesicles and inclusion bodies in both appear identical on micro copic section

Howard L Moscovitz reports a case that initiated a minor epidemic of classic chickenpox among 14 adults

Woman 67 had chronic lymphatic leukemia A week before hospitalization herpes zoster ophthalmicus developed Two days after h spitalization a satellite lesion appeared on the anterior chest and within 24 hours the skin was covered with innumerable umbilicated purplish red ten e vesicles and small bullae No area was spared Apparently generalized herpe zo ter developed in the course of leukemia The degree to which maintenance cortisone therapy altered the clinical picture was difficult to evaluate Alternative di agnoses were hemorrhagic smallpox and hemorrhagic leukemia cutis The temperature rose to 104 F She became severely toxic and died a week after appearance of the disseminated eruption

Three days after the patient had died—10 days after the disseminated eruption had appeared—chickenpox developed in a grandchild and in about a week in 10 of the hospital staff

(5) J Mt S H p 2 79 90 July A g 1955

spontaneous onset of labor and vaginal delivery were anticipated Poliomyelitis per se without respiratory involvement even with four extremity paralysis was not an indication for cesarean section Pregnancy was terminated only for obstetric indications except in a few patients with acute severe progressive bulbar spinal poliomyelitis which occurred four to six weeks before term

The attack rate of poliomyelitis in pregnant women was 1 9 times that in nonpregnant women a significant trend

The effects of maternal poliomyelitis on the fetus in utero were evaluated Most fetal loss probably would not have occurred except for the mother s disease Even mild nonparalytic poliomyelitis may cause abortion especially early in the first trimester Among the 325 patients with poliomyelitis there were 43 known abortions an incidence of 13% Infants of mothers who contracted poliomyelitis early in pregnancy tended to be subnormal in weight at term Two mothers who had poliomyelitis at 6 and 22 weeks respectively delivered infants with cardiac defects This incidence was insufficient to lend credence to viral damage to the fetus in the first trimester of pregnancy There was no evidence of intrauterine transplacental transmission of the poliomyelitis virus None of the infants delivered developed poliomyelitis

• [Here is good statistical basis on which to answer some of the questions that always come up when the pregnant woman contracts poliomyelitis —Ed]

Pathogenesis of Pulmonary Infections in Patients with Poliomyelitis Mark H Lepper Paul B Szanto Sidney Kofman George Gee Jackson and Harry F Dowling[4] (Univ of Illinois) studied several blocks of tissue from each lobe of the lungs of 27 patients who died within three weeks of onset of acute poliomyelitis A high incidence of pulmonary infection was found All patients had had a tracheotomy and artificial respiration had been necessary Careful bacteriologic studies were made on tracheal aspirations before death and on the blocks of tissue used for histologic study

Comparison of histologic and bacteriologic findings indicated a good correlation between occurrence of pulmonary infection of the bacterial type and occurrence of bacteria in the cultures The organisms involved were Micrococcus py

(4) Am J M S 230 270 275 S pt mbe 1955

Man 57 had chronic lymphatic leukemia for 10 years He was given blood transfusions and later vesicles appeared on the right chest wall in the distribution of the 9th thoracic spinal nerves Four days later chlortetracycline was begun and four days after that a rash appeared on the face arms and chest beginning as erythematous macules soon surmounted by vesicles filled with clear fluid bacteriologically sterile Many vesicles became hemorrhagic and secondarily infected with pyogenic staphylococci The eruption rapidly covered the entire body surface including palms and soles but without involving the mucous membranes The epidermis was necrotic at the site of the original herpetic patch Biopsy of a vesicle from the upper extremity revealed characteristic Lipschutz intranuclear inclusion bodies with focal accumulation of lymphocytes in the dermis Blood culture on the twenty second day were positive for Staphylococcus aureus and Pseudomonas aeruginosa On administration of penicillin streptomycin and chlortetracycline the fever cleared and he improved He later died suddenly

Fluid collected by capillary tubes from a number of widely separated vesicles on the extremities and trunk when the varicelliform eruption was at its height contained particles similar to the elementary bodies of herpes zoster in size shape central depression and inclusion of some of the bodies in a sticky matrix

• [The tendency to generalized dissemination of herpes zoster in patients with chronic lymphatic leukemia noted here and in the preceding article is interesting one wishes it could be explained —Ed]

VIRUS TISSUE CULTURE IN CLINICAL DIAGNOSIS

Tissue Culture Diagnosis of Poliomyelitis and Aseptic Meningitis Mary O Godenne and John T Riordan[7] (Yale Univ) emphasize the value of virus isolation and serologic (antibody) tests in the early diagnosis of poliomyelitis infection Between July and December 1954 96 adults and children with discharge diagnoses of paralytic poliomyelitis aseptic meningitis or nonparalytic poliomyelitis and encephalitis were studied Throat and rectal swabs cerebrospinal fluid and stool suspensions were inoculated into monkey kidney epithelial cell tissue cultures Serum antibody determinations on serums from acutely ill and convalescent patients were done by neutralization and complement fixation tests

The poliomyelitis virus was isolated from 60 (62 5%) of the 96 patients from 44 of 49 (90%) patients with paralytic

(7) J A M A 158 707 71 J ly 2 1955

who had been in contact with the patient or with her contacts including a resident doctor on the ward Two weeks after he had received vesicle fluid from the resident chickenpox developed in a laboratory technician On this day herpes zoster developed in a patient with myasthenia gravis who recalled having had chickenpox in childhood Chickenpox occurred in two other patients 22 and 33 days after the disseminated hemorrhagic rash had appeared in the original patient They were probably secondarily exposed via staff members rather than directly via the source

Laboratory studies on the vesicle fluid of the resident seemed to exclude smallpox vaccinia and herpes simplex As yet the infectious agent of herpes zoster or that of chickenpox has not been regularly cultivated in the laboratory Incidence of generalized herpes zoster is unusually high in patients with chronic lymphatic leukemia and to a lesser extent in the other lymphomas The reason for this is unknown

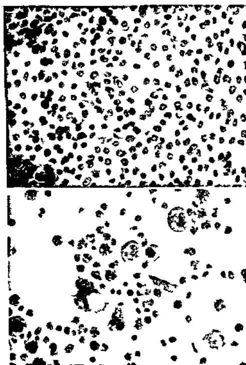
Average incubation period was 12 13 days The best index of the incubation period was the 14 days that elapsed between delivery of the vesicle fluid to the virology technician and the appearance of rash The virology laboratory is in a different building and the technician had no direct contact with the wards

Disseminated Herpes Zoster Complicating Chronic Lymphatic Leukemia Report of Case with Electron Microscope Study of Vesicle Fluid is made by Gerald P Rodnan and Geoffrey W Rake[6] (Brooklyn) Generalized dissemination is commoner when herpes zoster occurs in a patient with leukemia than if the infection occurs in an otherwise healthy person

Electron microscopy has revealed the elementary bodies of varicella to be brick shaped particles with an average length of 238 μ Similar observations have been made in herpes zoster The particles of herpes are most plentiful in fluid from vesicles 12 hours old or less disappearing rapidly from older lesions In the case presented fluid from widely disseminated vesicles contained particles indistinguishable from those of herpes zoster suggesting that the virus responsible for the primary herpes zoster was also involved in the subsequent disseminated varicelliform eruption

(6) New England J Med 254 472 474 Mar 8 1956

with stomatitis The causative agent of the virus infections was detected within 8 20 hours after tissue culture of rabbit corneal epithelium was inoculated with herpetic material Small laboratories doing virus research or diagnostic work



Fg 4 (t p) —N mal bbt l p th l m 4 d y g wth m t lt h m t l d d ed f m 154
Fg 5 (bottom) —Rabb t orn l t cultu 20 hou fte inoc lat on w th sal f om p tient w h tom t t h m t yl d eo edu d f m 154 Not gen l yt p th gen ffect d p f g t ll
(Court y f Doa F t l C d M A J 73 260 263 A g 15 1955)

can obtain rabbit tissue at moderate cost Diagnosis was confirmed in 10 of the 16 patients with suspected herpetic infections

Tissue cultures of rabbit cornea are as sensitive as inocula tion of the rabbit cornea in vivo for detecting herpes sim plex virus in patients with keratitis or stomatitis Figures 4 and 5 compare the tissue culture of normal rabbit corneal

poliomyelitis from 13 of 41 (32%) with aseptic meningitis including nonparalytic poliomyelitis and from 3 of 6 (50%) with encephalitis Among 31 patients with miscellaneous diseases none harbored the poliomyelitis virus In a few patients cytopathogenic agents as yet unidentified were encountered among the aseptic meningitis group

Poliomyelitis viruses were isolated in 89 100% of the stool specimens from paralytic patients but only in 43-49% of the throat and rectal swabs In 60% of the patients from whom the virus was isolated it was recognized and typed within seven days of inoculation

To be diagnostic neutralizing and complement fixation antibodies must be studied together for neutralizing antibodies may represent a persistent response to poliomyelitis infection acquired years before the present illness while complement fixation antibodies are more likely to indicate recent infection Of five patients with paralysis from whom virus was not isolated the antibody response was diagnostic in four In 12 patients with aseptic meningitis from whom virus was not isolated the serologic tests were suggestive of recent poliomyelitis infection Maximal complement fixation titers occur early in the disease and in 38 of the 57 patients harboring a poliomyelitis virus the first serum sample was diagnostically significant

The diagnosis of nonparalytic poliomyelitis is no longer guesswork Isolation of poliomyelitis virus is the most reliable test and results can be obtained in days Antibody studies are also indispensable especially if carried out on early and convalescent serum simultaneously Complement fixation an index of recent poliomyelitis infection is particularly useful

Rapid Diagnosis of Herpetic Infections by Isolation of Virus in Tissue Cultures Until recently laboratory diagnosis of herpes simplex depended on inoculation of animals or chick embryos but several days are required for results while the infection occurs in 24-48 hours Tissue cultures of rabbit cornea are susceptible to herpes virus and show histologic evidence of infection within a few hours

A rapid method of diagnosis is presented by Frances Doane A J Rhodes and H L Ormsby[3] (Toronto) who made laboratory studies on 16 patients 9 with keratitis and 7

(3) Canad M A J 73 260 263 Aug 15 1955

and hoarseness predominant are characteristics of ARD an acute febrile respiratory infection of short duration The condition was first described in military populations by the Commission on Acute Respiratory Diseases and can be distinguished from other acute respiratory illnesses such as the common cold streptococcic pharyngitis and tonsillitis and primary atypical pneumonia The etiologic agent was thought to be filterable and probably viral

Tonsils and adenoids grown in tissue culture have yielded cytopathogenic agents a new group of viruses that propagate in the upper respiratory tract of man which suggested a new approach to the investigation of acute undifferentiated respiratory infections During an epidemic of influenza like acute respiratory diseases at Fort Leonard Wood Mo in the winter of 1952 53 five strains of cytopathogenic agents were isolated by tissue culture Most patients had a rise in neutralizing antibodies against one of the strains i olated the RI 67 strain Isolation of this agent presumably a virus from patients with ARD presented the opportunity to establish the etiology of ARD and to determine the relation to the agents isolated by Rowe called adenoid degeneration agents obtained from human tonsil and adenoid tissue culture

Serums obtained from donors of infected respiratory secretions and recipients of these secretions during a human transmis ion experiment were tested for neutralization titrations with the RI 67 agent and the adenoid degeneration agents The acute upper respiratory infection ARD was caused by an agent presumably a virus identical with or closely related to the RI 67 agent The adenoid degeneration agents did not produce the illness

The study shows that ARD is a clinical entity distinct from the common cold or primary atypical pneumonia Other agents immunologically different from the RI 67 virus probably also cause ARD The authors propose that the RI 67 agent be called an ARD virus

• [In th s and the preceding article we see hand ome d vidends from the storage of acute and convalescent serums of persons with acute illnesses of unknown et ology In both instances it was possible to show development of antibodies against agents first recognized years after the patients were being treated How helpful it would be if someone had done this during the 1918 19 pandemic of influenza —Ed]

epithelium and that inoculated with saliva from a patient with stomatitis

• [Occasionally the rapid differentiation between generalized herpetic infection and smallpox is an urgent matter This kind of help would be invaluable under such circumstances —Ed]

NEW VIRUSES

New Type of APC Virus from Epidemic Keratoconjunctivitis is reported by E Jawetz S Kimura, A N Nicholas P Thygeson and L Hanna[9] (Univ of California) Epidemic keratoconjunctivitis is an eye infection with sharply defined clinical characteristics especially development of round subepithelial corneal opacities Until the present case no virus was known as the etiologic agent

Conjunctival and corneal scrapings obtained from a seaman with typical epidemic keratoconjunctivitis who had just arrived from the Orient revealed cytopathogenic changes on the 17th day of incubation and a transmissible agent was passed in HeLa cultures Serum from patients with well established typical epidemic keratoconjunctivitis were examined for neutralizing antibodies to the virus All 25 patients with typical clinical disease possessed neutralizing antibodies in a serum dilution of 1 10 or greater from four weeks to three years after onset of the disease Of 29 patients with other types of eye disease only two had such antibodies

The evidence indicates that the virus isolated from a typical case of epidemic keratoconjunctivitis belongs in the group of APC viruses but does not fit a hitherto established type No claim is made concerning its etiologic role but serologic evidence strongly suggests that the virus was regularly associated with typical epidemic keratoconjunctivitis from 1951 to 1955 in several localities in North America

Etiologic Relationship of the RI 67 Agent to 'Acute Respiratory Disease (ARD) was established by Harold S Ginsberg George F Badger John H Dingle William S Jordan Jr and Sidney Katz[1] (Western Reserve Univ) Both constitutional and localized respiratory symptoms with cough

(9) S ence 12? 1190 1191 Dec 16 1955
(1) J Cl n I est 34 8 0 831 Ju e 1955

had been an inmate of the Illinois State Penitentiary for the previous four years

Early acute symptoms were headache myalgia fever nausea and vomiting The physical examination was normal in most cases except for fever and tachycardia The white blood cell count often was depressed to 4,000 5 000/cc Six patients developed painful stiffness of the joints one to five weeks after the acute symptoms subsided but all six were clinically well during follow up periods of 4 31 weeks No cross infections were observed in any of these patients or in the nursing or medical personnel

The illness could be transmitted by plasma filtered through Berkefeld diatomaceous porosity N or W filters at a pressure of 660 mm Hg Blood samples drawn from one patient during 13 months follow up were repeatedly infectious

Of 37 men inoculated intravenously with fresh plasma red blood cells or whole blood from the original donor or from patients during the acute symptomatic phase 31 (84%) developed typical symptoms within 30 days The agent is probably viral Because it survives blood banking and may be present in healthy volunteers it represents another potential hazard in the transfusion of blood

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MYCOTIC INFECTIONS

Cerebral Mucormycosis—Pathogenesis of the Disease ***Description of the Fungus Rhizopus Oryzae Isolated from*** **a Fatal Case** is reported by Heinz Bauer Libero Ajello Elizabeth Adams and Domingo Useda Hernandez[4] (Emory Univ) This unusual and generally fatal complication of diabetes mellitus is characterized by uncontrolled diabetes with ophthalmoplegia and meningoencephalitis Specific treatment is not available At autopsy invasion of the meninges brain cerebral vessels orbits and paranasal sinuses by the fungus is usually found Case histories and autopsy findings are presented in two patients who followed this course Diagnosis was made in the first patient from histologic sections at autopsy but in the second patient

(4) Am J Med 18 8 2 831 M y 1955

Role of Swimming Pool in Transmission of Pharyngeal Conjunctival Fever During the first six months of 1955 H L Ormsby and W S Aitchison[2] (Toronto) examined about 20 adults with viral conjunctivitis Symptoms were unilateral follicular conjunctivitis during the first five days followed by involvement in the other eye The preauricular nodes on the affected side were variably enlarged and tender In about half the patients corneal opacities developed in the affected eyes and in seven of these washings from the affected eyes had a cytopathogenic effect in tissue cultures of trypsinized monkey kidney or HeLa cells The virus was identified as type III APC group

Beginning in August 1955 children began having similar conjunctivitis All of them had been in swimming pools The course was similar to the adult form but milder occurring first in one eye and then three to five days later in the other In only a few children were corneal opacities noted and they disappeared within a few weeks Pharyngitis and fever were present in most children with temperatures of 103 105 F for several days Muscle pain and catarrhal otitis media were frequent The disease was obviously transmitted in the swimming pools and incidence rapidly declined during the last two weeks of August when attendance at swimming pools was restricted

Washings from the eyes and throats of more than 50 patients were taken Identification of three of seven strains isolated from adults as type III APC virus suggests that the swimming pool epidemic was due to this virus

• [This appears similar to the findings of Jawetz *et al* (This YEAR BOOK p 68)—Ed]

Previously Unrecognized Transmissible Agent in Human Blood Experimental and Clinical Studies Ernest Beutler and Raymond J Dern[3] (Univ of Chicago) in studying erythrocyte survival injected cells from a single healthy donor into six subjects An influenza like febrile illness occurred in five about two weeks after the injection and serial transmission of blood collected during the acute phase of this illness caused a similar syndrome *in new recipients* The original source was an apparently healthy man aged 25 who

(2) Canad M A J 73 864 866 Dec 1 1955
(3) J A M A 159 989 994 Nov 5 1955

due to invasion of blood vessels by the organism with formation of thrombi and emboli Individual hyphae often occlude small blood vessels Meningitis is usually localized to the frontal lobes

Sinusitis was described in only three previous instances At autopsy routine histologic examination of the paranasal sinuses in patients with diabetes may show that this lesion is common Entry to the central nervous system may be by invasion of the ethmoid sinus mucosa and extension into the underlying tissue with involvement of bone Spread apparently is via blood vessels which are readily invaded

Signs of retro orbital infection usually unilateral culminating in ophthalmoplegia and of meningoencephalitis in patients with diabetes should suggest the possibility of cerebral mucormycosis Considering the high incidence of diabetes mellitus and the ubiquitous presence of mucorales the disease should be more commonly suspected than is reported

• [Here is a most interesting association between diabetes and a specific infectious disease —Ed]

Epidemic of North American Blastomycosis J Graham Smith Jr Jerome S Harris Norman F Conant and David T Smith[5] (Duke Univ) report 11 cases of this fungus disease diagnosed during a six month period all occurring in a small circumscribed area in North Carolina

The youngest patient was 5 months old and diagnosis was established after death at age 7 months The oldest was 77 years 7 were aged 16 or younger and 2 were aged 20 50 Five were female four were Negro and six lived on farms or had parents who lived on farms The homes of two patients were on land formerly used to raise tobacco and one patient raised vegetables in his back yard Five patients were of moderately well to do social background and five were from a lower income class

All the patients had pulmonary disease and only one had a skin lesion In general the symptoms were low grade fever cough malaise weight loss anorexia and inability to work Erythema nodosum appeared in three of the children an unusual manifestation not previously reported

Four children were treated with 2 hydroxystilbamidine and four adults with stilbamidine All responded to therapy

(5) J A M A 158 641 646 J 5 1955

diagnosis was suspected ante mortem and appropriate cultures and tissue samples were obtained (Figs 6 9)

Of the two present and nine previously reported patients all but four had diabetes mellitus and most were acidotic



Fig 6 (top left) Mid m d eb l l with th ml te n m u mycel m n th mbu s el w ll n i tr nd g t e Hem t yl n phl x di d fr m ×2 0

Fig 7 (top right)—Mycel m e b al o tex n t larg a rt t a d branching f gus Hematoxyl n phl n d d f om ×480

Fig 8 (bottom left)—Men g th r v el a d r b l rt h w h a infiltrat on by hyph e w th attend g fl mm tory c ll t on t th ombo of men ngeal v s l H m to yl phl i e r du ed f m ×95

Fig 9 (bottom right)—Right i t l c rot d tery w th m l th t s Many hyph e pr sent th o gh t v el wall a d n thr mb ll m yl n phlox e educed f m ×110

(C rt sy of B u r H et l Am J Med 18 82 831 M y 1955)

Typical sequence was appearance of ophthalmoplegia usually unilateral signs of meningoencephalitis and persistent hyperglycemia and glycosuria Neurologic manifestations usually appeared after diabetic acidosis had responded to therapy and the patients seemed clinically improved

Autopsy reveals multiple areas of infarction in the brain

great to be accidental but the nature of the association is unknown In the authors case the cryptococci probably were a terminal event in typical Hodgkin s disease The im munity mechanisms may be deranged in Hodgkin s disease and perhaps the e patients are peculiarly susceptible to cryp tococcic infection

* [Elsewhere in this section we have noted the association of disseminated herpes zoster and chronic lymphatic leukemia al o of mucormycosis and diabetes mellitus Here is a third example Increasing attention is being given to studies of host factors in infectious disease —Ed]

MISCEI LANFOUS INFECTIOUS DISEASES

Anthrax Report of 117 Cases Herman Gold[7] (Chester Pa) studied 116 cases of external or cutaneous anthrax and 1 of pulmonary anthrax during a 22 year period One pa tient died a mortality rate of 0 8%

Of the cutaneous cases 104 originated in a mill where goat s hair is used to make men s coat interlinings The goat hair was imported from China India Pakistan and Moroc co Six cases developed after use of contaminated bobbins and a truck driver had anthrax of the neck several months after hauling bales of hair

Trauma to the skin had occurred in many patients usual ly a minor scratch The early lesion looked like a flea bite or tiny pimple which turned brown on top and was surrounded by a ring of erythema By the second day shiny yellow vesi cles encircled the apex of the papule and painless nonpitting edema appeared and spread beyond the papule s vicinity On the fifth to eventh day a tough dry eschar covered the cen ter of the ulcer and spread into the crusting peripheral vesi cles The e char separated and oughed by the 12th to 14th day leaving a hallow ulcer that healed by granulation Figures 10 and 11 illustrate this stage

Itching at the site of the papule may be an early and striking symptom Some patients were asymptomatic but most had headache malaise and fever to 102 F or higher Blood counts were usually normal but a few patients had leukocytosis of 10 500 13 500 cells Blood cultures were ster

(7) A M A Arch I t M d 96 3 7 396 S ptembe 1955

with gradual resolution of the pulmonary lesions and negative sputums Before the introduction of this therapy the mortality was as high as 92% in patients with systemic involvement The 7 month old child died before treatment could be instituted and two adults recovered without therapy

North American blastomycosis is a disease limited to the United States and Canada A proved epidemic has not been reported before

Acute Disseminated Torulosis Associated with Hodgkin s Disease is reported by M Levene and L Michaels[6] (Manchester England) About 18 cases have been recorded in which a condition resembling Hodgkin s disease was associated with active torulosis Some authors have considered torulosis the etiologic agent in Hodgkin s disease

Woman 59 had had recurrent leg ulcers for eight years She developed a cough and basal congestion of the lungs The liver was enlarged and nodular and liver function was deranged The tip of the spleen was palpable Ascites appeared and the fluid contained cells interpreted as malignant and large numbers of encapsulated yeastlike organisms which were Cryptococcus neoformans

At autopsy the peritoneal cavity contained a large quantity of cloudy yellow fluid Lymph nodes were enlarged in the periaortic chain the hilus of the liver the transverse mesocolon and the pelvis The liver and spleen were moderately enlarged

Histologically liver nodules were islands of characteristic Hodgkin infiltration composed of enlarged reticulum cells multinucleate cells lymphocytes and fibroblasts The spleen and the enlarged lymph nodes had a similar histologic appearance Small collections of histiocytes in the brain meninges and the lungs contained cryptococci

Acute liver failure in this patient was probably due to the combination of widespread Hodgkin s lesions in the liver and portal cirrhosis The cirrhosis may have been present before the Hodgkin s disease developed

The overwhelming acute infection with cryptococcus may have been related to heavy antibiotic therapy during the last three months of life It is unknown whether antibiotics directly stimulate the multiplication of C neoformans as they do with Candida albicans

Some relationship must exist between Hodgkin s disease and torulosis since the number of cases described is too

(6) J Cl P th 8 201 206 A g t 1955

and had been present for several weeks to many months No fever had been noted but the debility was associated with malaise insomnia weakness and numbness of the lower limbs Frequent complaints were heaviness of the scrotum nocturnal pains in the inguinal region testes knees thighs or axillae and mental depression All patients had some enlargement of the lymph nodes most frequently the inguinal axillary and epitrochlear chains When inflamed the overlying skin was hot and sometimes adherent Inflammation of the genitalia was the commonest reason for hospitalization The spermatic cord was thickened and edematous often nodular with palpably enlarged lymphatic vessels All degrees of inflammation were noted from the mildest with few constitutional signs to the most severe with septicemia rigors delirium and abdominal rigidity

In 13 cases pus cells and organisms were found in the urine streptococci in 5 staphylococci in 4 and coliform bacteria in 4 Urinary infection was present in all patients who had chyluria filarial colic and peritonitis and in 41% with genital lesions Seven patients had chyluria which was intermittent and would have been missed in some if each urine specimen had not been examined The origin of lymphorrhea was not apparent in any case Three patients had abscesses of the lower limb but there was no evidence that they were due to the disease No adult worms or larvae were found in them The history was usually helpful in diagnosis Eosinophilia was generally present (5 15%) often with a moderate neutrophil leukocytosis Repeated blood examinations at night revealed microfilarae in only 13 cases

Leprosy in United States L F Badger[9] (U S P H S) reviewed the data on 1 463 patients 637 foreign born and 822 American born admitted to the National Leprosarium at Carville La since its opening in 1921 Most of the patients were admitted from the states of New York Florida Louisiana Texas and California but at least one patient was admitted from each of 40 states and the District of Columbia Thus the disease may appear in any section of the country Of the 158 patients admitted from New York 140 were of foreign birth and only 18 were born within the continental United States

As well as being largely confined to a few states leprosy

(9) P b H lth R p 70 5 5 535 J 1955

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Antianthrax serum was effective in treating the disease but prolonged and severe serum sickness occurred The sulfonamides penicillin streptomycin chloramphenicol tetracycline oxytetracycline chlortetracycline and erythromy



Fg 10 (l ft) —Typ l a th le th e t f u d y old C t r d y bla k a d s rou d d by ing f ve l th t co ta n hem rh g c fl d Pa le s d m s rou d th l on
Fig 11 (ght) – Fxte v ed m ro d g a th x l on
(Cou t sy f Gold H A M A A h Int Med 96 387 396 Septembe 1955)

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Early prompt recognition of anthrax is essential Treatment with penicillin or broad spectrum antibiotics in adequate doses offers the best chance of cure The disease must be treated systemically The broad spectrum antibiotics are easily administered and cause few or no reactions and allow ambulatory treatment of these patients Control of the spreading edema and subsidence of systemic toxicity are the criteria of adequate dosage

Clinical Aspects of Filariasis Robert Alhadeff[8] (Post grad Med School London) summarizes 33 cases seen in Mauritian troops stationed in the Suez Canal Clinical diagnosis was certain in all but microfilariae were not always found

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(8) J Trop Med 58 173 179 Aug t 1955

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Transmission of Infectious Hepatitis by Transfusion of Whole Blood With a Note on Early Appearance of Viremia in This Disease Infectious hepatitis is usually transmitted by person to person contact probably by the fecal oral route Blood stream invasion is probably common and may be an integral part of the infection The infection has been passed experimentally in humans with acute stage whole blood as the inoculum orally or parenterally administered A Gardner Harden Jeremiah A Barondess and Brent Parker[2] (New York) report two cases of infectious hepa titis transmitted during transfusion of blood not known to be infectious Viremia appeared earlier than has previously been recognized

CASE 1 —Woman 23 donated blood Two weeks later systemic symptoms developed followed in nine days by pale stools dark urine and icterus Laboratory tests confirmed hepatitis

CASE 2 —Woman 40 who had no history of jaundice biliary tract disease or previous injections received two transfusions during sur gery one donated by Case 1 Two weeks later a pruritic maculo papular eruption appeared on the 27th day she noted dark urine chilly sensations and nausea and on the 30th day she became jaun diced Laboratory tests confirmed hepatitis

The interval between transfusion and onset of illness in Case 2 was 14 days This interval and the interval between transfusion and the appearance of jaundice (30 days) are shorter than the incubation periods of serum hepatitis re ported from clinical practice and human experiments Both intervals are within the range of incubation periods de scribed for infectious hepatitis

Decompression Treatment of Whooping Cough Clinical Survey of 903 Cases For six years H Stanley Banks[3] (Lon don) treated whooping cough by low air pressure in a de compression chamber once or twice a week Only 782 686 of whom were out patients could be included in the study

Acutely ill patients especially with pyrexia cyanosis or more than minimal pulmonary collapse shown by x ray were not treated by decompression because they were unable to tolerate it As many as six or eight patients at a time went into the chamber accompanied by a nurse or ward orderly or parents of the infants or children The pressure in the chamber was reduced progressively for about 20 minutes un

(2) N w E gla d J M d 53 923 925 Nov 4 1955
(3) B t M J 1 1052 1055 Ap 30 1955

was limited to areas within these states Of 137 cases from Florida 44 5% were recognized in Monroe county Within Key West the disease was concentrated in one section of the city of the 65 patients from this city 39 lived within an area about five blocks square In Louisiana the disease was concentrated in the lower half of the state and in Texas in the southeastern portion In California the 521 patients had lived in 33 of the 58 counties 10 or more patients had lived in each of 11 counties and 293 lived in San Francisco or Los Angeles county

The concentration of leprosy in limited areas is important in many instances being related to the possible source of infection

Smallpox among Vaccinated Troops is reported by Harvey H Waldo[1] (Pusan Korea) Although all American military personnel have been vaccinated against smallpox and are considered immune to the disease some contract smallpox when exposed to the causative agent During the first six months of 1953 six patients were hospitalized with smallpox and four were American soldiers

Many American physicians have never seen smallpox and until they do are not suspicious Although four patients had an apparent rash on hospitalization in only one was smallpox suspected In five the referring diagnosis was not smallpox

Smallpox vaccination has been valuable Absolute protection is not to be expected Balance between virulence of the causative agent and degree of immunity determines whether infection occurs The disease was less severe in the three patients successfully vaccinated during childhood None of the six patients had had a recent successful vaccination and three had apparently never had a successful one

American soldiers are presumably vaccinated on induction and again before being sent overseas Errors in immunization can be entirely eliminated only if the physicians are charged with sufficient knowledge and interest A vaccination given correctly with a potent vaccine read at the proper time by trained personnel and properly recorded is the first line of defense against the disease

(1) U S Armed Fo ces M J 6 799 806 Ju 1955

Relationship of Immune Response to Group A Streptococci to Course of Acute Chronic and Recurrent Rheumatic Fever By immunochemical methods an antecedent group A streptococcic infection can be demonstrated in virtually every new attack of acute rheumatic fever Once a rheumatic attack has been initiated the disease may end abruptly become subacute or chronic or relapse at a later date Frequently it is not clear whether a given clinical cycle or exacerbation of the disease is the course of a single attack or whether the disease is being reactivated or perpetuated by subclinical streptococcic infection

Gene H Stollerman Arthur J Lewis Irwin Schultz and Angelo Taranta[4] (New York Univ) observed the clinical course of rheumatic fever in 580 hospitalized patients during a four year period The factor of streptococcic infection was closely evaluated by routine throat cultures at regular intervals and by serial determinations of serum antistreptolysin O antistreptokinase and antihyaluronidase During the first year continuous chemoprophylaxis was not given but the streptococcus was eradicated when detected by throat culture During the last three years all patients received continuous chemoprophylaxis

A high initial titer of antistreptolysin O antistreptokinase or antihyaluronidase was found in 95% of patients studied within two months of the onset of rheumatic fever In the studies made closer to the onset the figure approached 100% The rate of fall of the three antibody levels was unrelated to the subsequent clinical course of the rheumatic attack

After suppressive treatment of rheumatic fever with aspirin or cortisone the disease relapsed spontaneously without new streptococcic infection as late as eight weeks after termination of therapy In some patients with severe rheumatic heart disease relapses were observed after even longer latent periods In these however reappearance of C reactive protein and a rise of sedimentation rate tachycardia during

(4) Am J Med 0 163 169 F b a y 1956

til the equivalent of a height of 12 000 ft was reached This low *pressure was maintained for 45 minutes and then grad*ually increased during the 20 25 minute descent Total treatment time was 90 minutes If the first treatment failed retreatment was usually of no avail

Treatment of whooping cough by high flying began in Strasbourg in 1927 when air pilots took children in the paroxysmal stage to heights of 10 000 ft (3 050 m) From 1937 to 1939 small scale trials were carried out in Strasbourg Switzerland *Germany Holland Poland Spain* Uruguay Chile and a few in England

Of the 782 carefully selected and assessed patients 28 2% were markedly improved in four to seven days after decompression Gradual but probably significant improvement was noted in an additional 34 1% The others showed no more than the expected change at that stage of the disease Of the children who had vomited food more than once daily 57 7% stopped vomiting a few days after treatment and in another 20% vomiting was relieved

The mechanism of action of the treatment is unknown The low pressure of the inspired air seems to be essential as results are similar whether high flying or decompression chamber is used The deeper breathing induced may help clear mucus from bronchi and perhaps small collapsed areas are aerated in some undetermined way Leukocyte counts are not helpful in elucidating the mechanism

The good results have been attributed to psychologic factors Many parents have high expectations for success of the treatment and a certain amount of emotion is aroused in the patients by the novelty of the treatment

Treatment is nearly always useless before 2½ weeks after onset and less effective after the 6th week The acutely ill patient is almost always made worse Even when patients are properly selected one cannot predict who will benefit and who will not *Decompression is a physical treatment* that may exert in some unknown way a favorable influence on the course of the disease

• [Evaluation of any method of treating whooping cough has always proved difficult —Ed]

streptococci of 75 patients receiving sulfadiazine 8 had positive cultures of 99 receiving penicillin orally 13 had positive cultures The antistreptolysin O serum titer determined every four weeks in patients receiving benzathine penicillin injections showed a significant rise in only three patients Evidence of progression of heart disease appeared in only 3 of the 145

A total of 4 871 injections of benzathine penicillin was administered to 410 patients the average being about 12 per patient Deep muscle soreness and tenderness for one to three days occurred in most patients Transient low grade fever was associated with local pain and tenderness in about 10% of the patients Penicillin hypersensitivity reactions occurred in five Three had mild generalized urticaria one urticaria and angioneurotic edema of the face and hands and one serum sickness reaction with fever angioneurotic edema and polyarthralgia

In two patients subacute bacterial endocarditis developed and Streptococcus viridans was isolated from the blood of each The strains of Str viridans isolated were sensitive to 0 1 and 0 3 unit of penicillin/cc culture medium

• [The authors make a strong case for this preparation as the best available for chemoprophylaxis against rheumatic fever Their reported incidence of sensitivity reactions (only about 1%) is surprisingly low of course much depends on their criteria and opportunity for continuous observation. Of interest is the occurrence of bacterial endocarditis due to penicillin sensitive Str viridans in two patients who were receiving penicillin prophylaxis —Ed]

Rheumatic Heart Disease in Scarlet Fever Patients Treated with Penicillin Follow up Study After Seven Years Penicillin therapy has reportedly prevented the recurrence of rheumatic fever when given to rheumatic subjects with an established streptococcic infection and reduced the incidence of rheumatic fever in normal adults with streptococcic pharyngitis In 1950 Weinstein Bachrach and Boyer suggested that penicillin therapy of scarlet fever did not appreciably reduce the frequency of rheumatic fever Rheumatic carditis as shown by abnormal ECG s appeared in 7% of 167 patients after a latent period Louis Weinstein Norman H Boyer and Martin Goldfield[6] (Boston Univ) re examined 110 of these patients seven years later

(6) New E gl d J M d 253 1 7 J ly 7 1955

sleep or fever indicated a relapse within two months of withdrawal of aspirin and cortisone

Every relapse of frank rheumatic activity that appeared more than two months after apparent complete subsidence was associated with evidence of antecedent new group A streptococcus infection Recurrences were not observed after a wide variety of acute infectious diseases bone fractures immunization procedures or intravenous injections of typhoid vaccine

• [There has been a considerable amount of debate over the point whether recurrence of rheumatic activity can be induced by stresses other than streptococcic infection This experience provides argument for the negative side —Ed]

Prophylaxis against Group A Streptococci in Rheumatic Fever Use of Single Monthly Injections of Benzathine Penicillin G Gene H Stollerman Jerome H Rusoff and Ilse Hirschfeld[5] (New York) treated 145 rheumatic fever patients for an average of about 20 months each The two year study confirms that monthly injections of benzathine penicillin offer a highly effective safe and practical prophylaxis against rheumatic recurrences

The major limitation of continuous oral chemoprophylaxis is that patients forget to take medication regularly Parenteral injections of penicillin afford a more reliable method In single monthly injections benzathine penicillin protects against group A streptococcus infections Frequency of rheumatic recurrences in patients receiving benzathine penicillin was compared with that in patients of similar age geographic distribution and stage of illness treated with other forms of prophylaxis

Rheumatic fever did not recur in any of the 145 patients Of 111 comparable patients taking 200 000 units of penicillin per day orally 2 had rheumatic recurrences of 73 patients receiving *1 Gm sulfadiazine daily 5 had rheumatic* recurrences All patients with recurrences while receiving daily oral prophylactic medication admitted frequent breaks in the regimen due to forgetfulness

Of 2 716 throat cultures (usually one culture per patient) made from patients receiving benzathine penicillin only 3 were positive for group A streptococci Of 269 patients in an untreated control group 52 (19 3%) harbored group A

(5) New England J Med. 52 787 792 May 12 1955

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(6) *New England J Med. 253 1 7 July 7 1955*

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(5) New England J Med 25 87 792 May 1 1955

after a latent period following a recent streptococcic infection probably indicates rheumatic carditis even if major signs are absent

* [This report is disturbing and cannot readily be reconciled with the very favorable results noted by Rammelkamp and his associates in military personnel in whom there seemed to be a highly significant reduction in incidence of rheumatic heart disease when streptococcic sore throat was treated with penicillin Since there has been almost universal acceptance and general application of these studies further attempts to secure a definitive answer are urgently indicated --Ed]

Natural Course of Active Rheumatic Carditis and Evaluation of Hormone Therapy Current opinions on effect of hormone therapy in rheumatic carditis are controversial May G Wilson and Wan Ngo Lim[7] (New York Hosp Cornell Med Center) reviewed the records of 100 randomly selected patients from the active file of the cardiac clinic These patients had experienced 165 observed attacks of active carditis between 1930 and 1955 of remarkably constant duration and severity Average duration of active carditis was less than two months in 20% of the attacks two to four months in 30% and four months to over a year in 50%

From 1949 to March 1955 55 patients with active carditis of 3 21 days duration were given hormone therapy Comparison of symptoms and signs of active carditis in the control and hormone treated groups before therapy reveals that those in the treated group were slightly more severe The hormones used were ACTH cortisone and hydrocortisone and average duration of therapy was seven days They were administered every six hours as follows corticotropin intramuscularly 25 unit for four days and 20 units for three days cortisone orally 100 mg for four days and 80 mg for three days hydrocortisone orally 80 mg for four days and 60 mg for three days

After completion of therapy most patients in whom it was started in the third week developed transient fever or joint pains on the fourth to the seventh day In three patients transient symptoms of carditis were observed which regressed spontaneously In six patients who had received inadequate therapy carditis recurred within 24-72 hours This was terminated by a second course of hormone therapy lasting seven days All patients were ambulatory within two

(7) J A M A. 160 1457 1460 Ap 28 1956

Of 12 patients who were thought to have rheumatic fever 11 had had symptoms of pharyngitis less than 48 hours before penicillin therapy was begun Ten of these were included in the 110 studied seven years later The 100 patients who were not suspected of having rheumatic fever had normal or borderline ECG s and no clinical manifestations of the rheumatic state on follow up

None of the 10 patients with suspected rheumatic fever in 1946 had any illness resembling rheumatic fever in the intervening seven years and none had had chemoprophylaxis Physical and x ray signs were consistent with rheumatic heart disease in six Four had mitral systolic and rumbling low pitched mitral diastolic and presystolic murmurs Two had aortic as well as mitral valvular disease Two other patients who had abnormal ECG s in 1946 were classified as having probable rheumatic heart disease seven years later The two remaining patients were considered to have entirely normal hearts on physical and x ray examination

The data suggest that penicillin therapy of acute streptococcic pharyngitis did not appreciably suppress the development of rheumatic heart disease Clinical features of acute rheumatic fever were so altered by antibiotic therapy of the initiating streptococcic infection that most of the striking manifestations of the rheumatic state did not develop and prolongation of atrioventricular conduction became the outstanding feature

Opinion regarding effect of penicillin therapy in suppressing rheumatic fever after streptococcic pharyngitis has differed one reason being the differences in ages of the groups studied In the age group reported here susceptibility to acute rheumatic fever is highest Older age groups reported on by other authors have a decreased susceptibility to acute rheumatic fever which may explain the relatively low prevalence of rheumatic fever in this group Another obvious difference is the criteria used for diagnosis of rheumatic fever In this series rheumatic fever was suspected primarily because of prolongation of atrioventricular conduction In other studies the diagnosis was made only if the criteria of Jones were fulfilled

A prolonged atrioventricular conduction time developing

patients In 26% the joints were abnormal by x ray The mo t frequent changes were soft tissue atrophy and osteo poro is of minimal degree

No one specific radiologic feature is distinctive of systemic lupus erythematosus but its pre ence can be strongly sus pected by roentgen studies Serial x rays of the chest are helpful The x ray constellation is almost diagnostic al though each individual x ray in itself may not be character istic

The most constant feature is pleuritis usually minimal bilateral and fibrinous Pneumonitis is the most perplexing

PLEURAL INVOLVEMENT IN 100 CASES OF SYSTEMIC LUPUS ERYTHEMATOSUS

T	R H S	L FT S	B LA RAL	TOT
Pleuritis	11	6	43	60
Small effusion	3	5	8	16
Massive effusion	1	1	0	2
Loculated effusion	3	0	0	3
Total	18	12	51	81

Seven p t ent l t d tw bec f b lat l l m t w th d ffering types f eact on g loculat on ght pleu t b lat ral

element of the constellation Clinically lingering pneumo nitis with low grade fever and no apparent response to anti biotics so frequently suggests virus pneumonia that this error is virtually a characteristic feature of the patient s history

A third feature is cardiac involvement with startling vari ations in heart size in a number of patients A fourth feature is joint change with incongruity between the x ray findings of minimal osteoporosis and soft tissue atrophy and the clin ical history of disabling painful hot and swollen joints The fifth feature is a slightly enlarged spleen

Treatment of Systemic Lupus Erythematosus with Pred nisone and Prednisolone was compared with the older ste roids by Alfred Jay Bollet Stanton Segal and Joseph J Bunim[9] (Nat l Inst of Health) in 10 patients whose disease had not been adequately controlled at the time of admission

(9) J A M A 159 1501 1507 Dec 17 1955

or three weeks of beginning therapy Active carditis lasted *less than one month* after onset of illness in two thirds of the patients and less than two months in the rest in marked contrast to the control group in most of whom it lasted *more than two months*

In 84% of the hormone treated group there was no residual cardiac enlargement or valvular lesions During the follow up *period of six months to five years murmurs regressed* in two thirds of the treated patients compared to only one third of the controls

The pattern of *rheumatic carditis has not changed* in the past 25 years Increasing cardiac chamber enlargement or the appearance of new murmurs rarely occurred in the absence of an overt attack of active carditis Evaluation of therapy does not require several years of follow up study The mechanism of hormone therapy in this disease is unknown In patients receiving hormone therapy the acute inflammatory phase is arrested within *24 72 hours* further *irreversible damage probably does not occur The later therapy* is instituted the greater is the chance of irreversible damage

* [By far the most optimistic statement on the value of hormone therapy in acute rheumatic carditis encountered —Ed]

COLLAGEN DISEASES

Roentgenologic Findings in Systemic Lupus Erythematosus Analysis of 100 Cases is presented by David M Gould and Marvin L Daves[8] (Johns Hopkins Univ) The commonest finding was pleural involvement present in 74 patients (table) *Bilateral pleural involvement present in 51%* is an important differential feature because pleural reaction due to tuberculosis infarct and carcinoma is much more likely to be unilateral

Parenchymal pulmonary involvement present in 50 patients was *considered to be directly caused by systemic lupus erythematosus* Usually the lesion was focal patchy infiltration but a significant number of linear plaques was encountered Cardiac involvement was present in 53% of the

(8) J Ch on D 2 136 145 Augu t 1955

It is not certain that simultaneous use of antimicrobial drugs prevents progression and dissemination of tuberculosis by ACTH or cortisone Several animal experiments and a few clinical studies suggest that this is so If combined therapy is safe ACTH and cortisone may be used more widely in tuberculosis for nontuberculous indications and case reports bearing on this question are worth while

A patient with far advanced cavernous pulmonary tuberculosis was given streptomycin and PAS Because of coexisting disseminated lupus erythematosus ACTH was started three weeks later Within eight weeks of hormone therapy the extensive bilateral exudative disease cleared remarkably the cavity closed without collapse procedures and the sputum became negative Results of the tuberculin test were negative to first strength while the dose of ACTH was greater than 30 mg daily All symptoms except sputum cleared in the first few days of treatment and that declined over several weeks

Despite numerous reports of deleterious effects of ACTH and cortisone on tuberculosis in experimental animals and association of reactivations serious spreads and disseminations in man these drugs have not been shown to be harmful in human tuberculosis when streptomycin and PAS are also administered

If streptomycin and PAS prevent the adverse effects of ACTH and cortisone on tuberculosis the steroids could be more widely used They would be advantageous in treatment of tuberculosis by symptomatic relief in the acutely and desperately ill patient and by inhibiting excess granulations and fibrosis

Discoid Lupus Erythematosus Analysis of Its Systemic Manifestations is made by Edmund L Dubois and Stuart Martel (Univ of Southern California) Chronic discoid lupus erythematosus has been considered primarily a skin disease with rare systemic manifestations To determine the truth of this theory the authors recorded a complete history made a physical examination and performed routine laboratory work on 41 patients with the disease The patients were separated into a group displaying the localized discoid form (26) with skin lesions above the chin and one with the generalized discoid form (15) howing cutaneous involve

( ) A I t M d 44 48 496 M h 1956

Prednisone and prednisolone were potent suppressive agents diminishing the fever chills malaise anorexia arthritis rash mucous membrane lesions cough pleuritic and precordial pain chest wall tenderness pleural and pericardial friction rubs pulmonary rales abdominal pain and tenderness headache convulsive seizures leukopenia elevated sedimentation rate and C reactive protein Renal abnormalities proteinuria microscopic hematuria cylindruria and azotemia improved only if the abnormalities had increased or appeared during an acute exacerbation usually with fever and dehydration Serious renal disease was not influenced and two patients died of uremia Blood pressure was not significantly altered Edema gradually diminished during prednisone therapy Leukopenia improved in most patients anemia did not and serum albumin and globulin were only slightly altered

Prednisone and prednisolone were about four times as potent as cortisone and hydrocortisone but caused no retention of salt or water or loss of potassium In general they closely paralleled cortisone and corticotropin in effectiveness and limitations Minor undesirable side effects in all 10 patients included minor mental changes transient euphoria and irritability facial rounding amenorrhea mild hirsutism epigastric discomfort and acneform eruption

• [These steroids are coming into greater use and to a considerable extent are supplanting cortisone and hydrocortisone The main advantage seems to be in the lessened (but by no means absent) tendency to cause edema On the other hand such serious consequences as psychosis glycosuria and peptic ulceration are at least as frequent as with cortisone — Ed]

Treatment of Patient with Lupus Erythematosus and Pulmonary Tuberculosis with ACTH Streptomycin and Para Aminosalicylic Acid is reported by J Richard Johnson and Winthrop N Davey[1] (Ann Arbor Mich) Cortisone and ACTH are regarded as contraindicated in tuberculosis because of suppression of inflammation granulation tissue formation and fibroblastic repair They have been reported to enhance tuberculosis in experimental animals and to reactivate or cause progression of pulmonary tuberculosis in man Pulmonary or disseminated lesions have occurred in some persons not previously known to have tuberculosis

(1) A I t Med 42 1109 1117 May 1955

Of the 61 patients of whom 30 continued on cortisone and 31 on aspirin 58 were clinically reassessed at the end of two years X ray films of the hands and feet were taken and sedimentation rates and hemoglobin levels were determined No significant differences were found between the two groups ✓

• [It seems worth while to lay great emphasis on this kind of report When one considers all the serious consequences that can result from long term steroid therapy contrasted with the comparative harmlessness of salicylates there should be great reluctance to beginning treatment of this chronic disease with steroids —Ed]

DISEASES OF UNCERTAIN ETIOLOGY

Acute Idiopathic Myocarditis an acute or subacute inflammation confined to the myocardium not affecting the pericardium endocardium or any other organ is of unknown etiology Other terms used for the condition are Fiedler s myocarditis or diffuse isolated circumscribed interstitial nonspecific or primary myocarditis It is generally reported in apparently healthy persons

Some authors object to classifying Fiedler s myocarditis as an etiologic pathologic or clinical entity Cases have been reported histologically indistinguishable from myocarditis that were associated with infections of the upper respiratory tract or with allergic reactions The cause probably varies but is predominantly from a myotrophic virus resembling the influenza viruses

Treatment includes the usual regimen for cardiac insufficiency Cortisone and corticotropic hormones seem to check the acute manifestations of myocarditis of rheumatic origin Garrison and Swisher reported a case apparently improved by cortisone In the case reported by Viggo Faber and Simon Fischer[4] (Copenhagen) the hormones caused transitory improvement but the patient died from cardiac insufficiency despite intensive therapy

Woman 35 had pains in the left thorax increasing difficulty in breathing and a dry cough for eight days She was severely ill pale and sweating orthopneic cyanotic and had left pleural effusion White blood cell count was 15 000 The heart appeared enlarged in x rays and an ECG showed low voltage ACTH and cortisone treatment was started The next morning her condition was improved with less dyspnea but in the afternoon she became worse She became more and more anxious and died 10 days after hospitalization

(4) A t m d sc d 154 135 138 1956

ment of the face and elsewhere Sixteen patients (62%) in the localized discoid group at some time in the course of their illness showed evidence by history and physical examination alone of arthritis fever Raynaud s phenomenon pleurisy or other systemic changes Fourteen patients with generalized discoid disease had such changes If in addition such laboratory abnormalities as leukopenia, elevated sedimentation rates hyperglobulinemia or abnormal flocculation tests results were considered 24 with localized disease and all with generalized disease showed these changes Therefore there was evidence of systemic involvement in 96% of patients with chronic discoid lupus

Three different modes of onset of discoid lupus were found Thirty three patients (72%) had cutaneous changes initially followed in 45% of this group by rheumatoid like arthritis Rheumatoid arthritis had occurred in seven patients before the appearance of discoid lesions One patient had biologic false positive serologic test reactions before skin lesions developed

Classification of lupus erythematosus is arbitrary as there are many transitions between the types Discoid lupus from its inception is a systemic disorder which is a variant of the more malignant acute disseminated form The benign appearing cutaneous lesion may herald advanced systemic manifestations that may be present at the same time or later when the skin changes have healed All patients should have a thorough general medical survey The form of therapy depends entirely on the extent of the disease

• [There is no question whatever that some patients who are thought to have discoid lupus eventually develop the systemic form however the criteria employed here for evidence of systemic disease seem very broad and the impression conveyed by the 96% figure could be misleading —Ed]

Comparison of Cortisone and Aspirin in Treatment of Early Cases of Rheumatoid Arthritis Second Report is presented by the Joint Committee of the Medical Research Council and Nuffield Foundation on Clinical Trials of Cortisone ACTH and Other Therapeutic Measures in Chronic Rheumatic Diseases[3] The first report on a study of 61 patients concluded that there was little difference between cortisone and aspirin in the early stages of rheumatoid arthritis The present report extends observations to two years from the beginning of therapy

(3) Brit M J 695 700 Sept 17 1955









F g 12 (pp l ft) —El ph t n t as P t t bo in E gla d had b n t t th t ou t y l ococ m t my t w l t d f m gu l gl d j d g tta k f lymph g t

F g 13 (pp ght) —El ph nt ost s P t t b n n P t g l C b d l ft th t y

F g 14 (l w l f) —P t f m p f Aq l Italy h d b t f I ly All l bo t y t g t on f fil l f t n w n g t M ococ m t my t w l t d d g py l tt k f om lvr ph t g l gla d

F g 15 (l w ght) —M ococ m t my t d d f m ×750 (C te y f C t ll A D m t l g 110 215 6 M M y 195)

At autopsy the lung contained a large hemorrhagic infarct The heart was flabby weighing 350 Gm There were no thrombi in the coronary vessels The myocardium was characteristically mottled with yellow areas of necrosis hyperemic portions and interstitial hemorrhage Essential histologic changes were found only in the myocardium consisting of widespread inflammatory infiltrations mostly lymphocytes and plasma cells with fewer neutrophilic and eosinophilic leukocytes Some of the muscle fibers were completely destroyed There was no sign of rheumatic arteritis Aschoff Stein granuloma or tuberculous necrosis No tubercle bacilli or gram positive cocci were observed and staining with congo red revealed no amyloidosis The endothelium of the vessels showed no virus inclusion bodies thrombosis or notable degeneration of the smaller vessels

• [The statement that this entity is predominantly due to a virus resembling influenza viruses seems unwarranted —Ed]

Elephantiasis Nostras Similarity of Its Clinical Symptomatology and Pathology with Elephantiasis Tropica vel Filarica is described by Aldo Castellani[5] (Lisbon) The term elephantiasis denotes any enlargement and deformation of a part of the body due to hypertrophic fibrosis of the skin and subcutaneous tissues The elephantiases may be classified as elephantiasis tropica (elephantiasis filarica) due to Wuchereria bancrofti (Filaria bancrofti) and Wuchereria malayi (Filaria malayi) elephantiasis nostras (elephantiasis non filarica elephantiasis bacterica) due to bacteria elephantiasis symptomatica pseudo elephantiasis caused by syphilitic frambetic tuberculous porozdenitic neoplastic or post operative lymphatic blockage and elephantiasis congenita Morbus Meige Milroy congenital and familial

The symptoms and course of elephantiasis nostras are identical with those of elephantiasis tropica filarica The disease begins with lymphangitis usually of the leg with high fever and the patient may feel very ill and prostrated Red erysipelas like patches appear on the affected limb often linear or in streaks The limb becomes edematous and may be painful and tender The inguinal glands are generally enlarged and painful The attack lasts two or three days or longer The swelling may disappear and limb size become normal after the first or second attack but after repeated attacks the limb becomes more and more swollen while the natural folds become exaggerated by the tumefaction on either side forming deep sulci The dorsum of the foot be

(5) Dermat log 110 215 6 Ma May 1935

delirious and had episodes of motor excitement The cerebro spinal fluid usually contained 10 100 cells the protein was increased and the sugar normal None of the patients died On discharge all seemed mentally normal and without neu rologic residua

The true incidence of rubella at any time and location is difficult to establish and the frequency of cerebral involve ment cannot be estimated but is probably rare Neurologic complications are more likely to follow certain epidemics Four of these eight cases occurred in an epidemic during the first five months of 1955 The frequency of permanent residua is unknown but permanent diplopia personality change psychic derangement and ataxia have been reported

Rubella encephalitis is classified with the group of so called postinfection encephalitides together with encephali tis following measles chickenpox mumps smallpox and vaccinia

Rubella Encephalitis is discussed by Poul Schleisner Jon Thorsteinsson and Ib Bøgeskov Jensen[7] (Horsens Den mark) who observed 4 hospitalized patients during the first months of 1955 and reviewed the reports of 75 patients with definite rubella encephalitis recorded in the literature

Neurologic symptoms usually appear three or four days after the appearance of exanthema which is characteristic of the acute onset of severe encephalitis Fever headache con vulsions coma stiffne s of the neck altered reflexes positive Kernig sign vomiting bulbar symptoms drowsiness con fusion respiratory difficulties positive Babinski reflex urine retention and alterations of the pupil occur with varying fre quency Visual disturbances conjugate deviation extra pyramidal and cerebellar symptoms nystagmus and paresis are rare The spinal fluid is clear and usually under normal pressure One third of the patients have no pleocytosis and in the others the cell count predominantly lymphocytes is only slightly increased The leukopenia usually accompany ing German measles is changed to leukocytosis of 10 000 20 000 when encephalitis occurs The course is rapid with complete recovery in most patients but death occurs in about 20% The fatal cases had pronounced hyperpyrexia which may have been the decisive factor

At present the only treatment is symptomatic Antipyret

(7) D h M B II 2 101 106 J ly 1955

comes swollen and puffy separated from the swollen lower leg by the deep ankle sulcus The leg may reach enormous dimensions (Figs 12 15)

After some years the attacks of fever may cease but the leg remains unchanged Spontaneous cure never occurs The lower limbs are most commonly affected, the scrotum frequently upper limbs seldom and the face and lips occasionally

Elephantiasis nostras cannot be differentiated clinically from filarial elephantiasis In each repeated attacks of lymphangitis is followed by temporary edema then solid edema and finally pachydermia with fibrotic hypertrophy of the skin and subcutaneous tissue

In elephantiasis nostras the blood never contains microfilariae and shows no eosinophilia In filarial elephantiasis microfilariae are also not found in many cases and eosinophilia is not a constant finding The diagnosis of elephantiasis nostras depends chiefly on the history of the patient s contracting the disease in a country where filaria is absent and on negative reactions to serologic and skin tests for filaria

Many authorities believe that elephantiasis nostras is caused by gram positive streptococci which enter the lymphatics through small wounds such as cracks between the toes in tinea pedis In 8 of 23 cases investigated bacteriologically cultures from inguinal glands and unbroken soft lymphatic skin nodules grew a delicate coccus or coccobacillus gram negative at first To this organism Castellani has assigned the name *metamyceticus* (Fig 15)

• [The causative relationship of Castellani s bacterium is certainly not established but there is no question that this clinical picture can be produced by infections other than filariasis —Ed]

NERVOUS SYSTEM MANIFESTATIONS

Encephalitis Following Rubella Report of Eight Cases is made by M Borch Jørgensen[6] (Copenhagen) The interval between exanthem and the onset of encephalitis ranged from one to six days mean three days The sensorium was affected in all the patients with variations from moderate torpidity and somnolence to deep coma Six patients were

(6) D b M B ll 2 106-110 J ly 1955

and sciatic neuritis transverse myelitis and paralytic bulbar forms akin to poliomyelitis The reports mainly concern Weil s disease and the neurologic complications apparently were not a feature of canicola fever In the author s case Leptospira canicola infection was followed by cervical radiculitis

A man aged 42 became ill a week after contact with a sick puppy Serum agglutination titers in the patient and the puppy were positive for Lept canicola A week after discharge from the hospital he noted aching in the shoulders followed by weakness of the right shoulder muscles and inability to raise the arm above the shoulder He had a sensation like sunburn over the outer aspect of the left forearm and weakness of the left thumb Examination revealed paralysis of the right serratus anterior muscle and winging of the scapula The left thumb was weak particularly in extension and abduction No other objective findings were present in the central nervous system or elsewhere

With physical therapy the thumb recovered and he was able to raise the right arm but the serratus anterior remained paralyzed six months after onset of illness X rays revealed a partially paralyzed right diaphragm

The neurologic signs and symptoms suggested bilateral patchy involvement of either the cervical segments of the spinal cord or its roots or nerves and the clinical picture closely resembled the shoulder girdle syndrome or neuralgic amyotrophy described by Parsonage and Turner Perhaps this close similarity indicates a common cause

Injury was not responsible for muscular paralysis in this patient To postulate a virus infection as the cause invokes a dual etiology Injection therapy was not used and the only drugs given were chlortetracycline barbiturates and compound codeine tablets Thus it is reasonable to presume that Lept canicola induced an antigen antibody reaction presenting as the shoulder girdle syndrome

Caramel Test of Cerebrospinal Fluid is reported by A Sole[1] (Vienna) Blood sugar level in tuberculous meningitis is lowered in contrast with all other types of serous meningitis For estimating the sugar content in cerebrospinal fluid Sole recommends autoclaving 3 5 cc fluid for an hour at 1 5

(1) Deutsch med W h sch 80 869 J 3 1955

ics previously used have recently been supplemented by cortisone and chlorpromazine the latter one of the most valuable antipyretics known The cortisone and chlorpromazine undoubtedly saved the life of one patient in whom the temperature steadily rose to 107 6 F despite the use of antipyrine and penicillin

• [It is interesting that the cases described in the preceding two articles were all seen in Denmark in 1955 There is reason to suspect that rubella is a group of diseases and on this occasion we seem to have had *an infection with an unusual tendency to affect the brain—Ed*]

Guillain Barre Syndrome as Manifestation of Infectious Mononucleosis Report of Case is presented by John Q Durfey and John L Allen[8] (Cincinnati Children s Hosp) As far as known this is the first reported case of its type The child showed a typical picture of the Guillain Barre syndrome in which the only manifestation of infectious mononucleosis was a markedly positive heterophil antibody titer The primary manifestation was severe central nervous system disease which appeared to be a separate entity in itself Infectious mononucleosis should be considered as a possible cause of neurologic disorders of unknown origin even in absence of so called typical signs and symptoms

Girl 4 had weakness of the left arm Examination revealed head drop *generalized weakness of almost all muscle groups and normal* cerebrospinal fluid The next day all deep tendon reflexes were absent and weakness progressed White blood cell count was 12 400 with 93% neutrophils and 7% lymphocytes No abnormal cells were seen She had two convulsions Dysphagia and dysphonia developed Tracheotomy was performed and she was placed in a tank respirator She then gradually improved Eight days after hospitalization cerebrospinal fluid protein level was 70 mg /100 ml A heterophil antibody titer about two weeks after admission was positive in a dilution of 1 1 792 Repeat titer a week later was positive in a dilution of 1 448 with a guinea pig kidney absorption test She recovered completely

• [The unique feature here is not the Guillain Barre syndrome which has been described before in infectious mononucleosis but the fact that there was no symptom or hematologic feature except the heterophil antibody reaction to suggest infectious mononucleosis —Ed]

Canicola Fever with Neurologic Complications is reported by J E Middleton[9] *(Sheffield) Neurologic complications* of the leptospiroses include subarachnoid hemorrhage paralysis of the palatal facial and oculomotor nerves brachial

(8) N w E a d J M d 54 7 0 F b 9 1956
(9) B t M J 2 5 6 J 19

fences and thorny material buried in clothing The incubation period in man ranges from three to seven days The lesions may be single or multiple and are usually on exposed parts especially the upper limb and face The lesion is first a dark red papule but in a few days it becomes larger umbilicated and covered with sodden looking skin

Differential diagnosis includes milkers nodules which are more often multiple purely nodular yellow turning to pink and come from cows molluscum contagiosum which is usually multiple pearly and pale and rarely attains the large size of orf cowpox or vaccinia which has no nodular forms but only a papule and becomes vesicular and pustular anthrax which has an intense inflammatory induration around a lesion which progresses from a papule to a bulla breaks and is followed by a dark eschar and herpes simplex

Orf is self limiting No known treatment definitely shortens its natural course

Durban Mystery Disease Report on Outbreak of Similar Nervous Disorder During the late summer of 1954 55 J Craig Cochrane and F M Vorster[3] (Transvaal) observed 10 patients with an unusual paralytic and anesthetic nervous condition resembling in many aspects Durban mystery disease As in Durban disease results of all investigations—bacterial viral and agglutination—were negative Rapid recovery of the gross incapacity was the rule within a week Relapses were frequent

Differential diagnosis includes anterior poliomyelitis Coxsackie virus infection hysteria Guillain Barre syndrome (infectious polyneuritis) and the group of diseases called Icelandic disease Adelaide Coventry Middlesex Hospital New York State epidemic and Durban mystery diseases

Features of patients with this group of diseases and of those in the present series are similar There is persistent relation to the poliomyelitis season Minor constitutional disorders such as sore throat and gastric upset frequently occur one to two weeks before paresis Onset of weakness is sudden and the patient describes the loss of normal limb function with difficulty as heaviness or an ebb and flow of power The muscles contract in a curious interrupted and clonic like fashion and response to effort is unsteady Simul

(3) M P oc 2 9 14 J u ry 1956

atmosphere gauge pressure Due to conversion of glucose into caramel the fluid changes to a brownish color the intensity of which corresponds to the amount of sugar present If the latter is low (40 mg /100 ml or less) the fluid remains almost colorless whereas with normal sugar content the color is light brown The caramel test is easily done

• [This rough screening test might be handy in the middle of the night —Ed]

SECTION ON FASCINATING NAMES

Orf, a virus infection of sheep known as scabby mouth or ecthyma contagiosum is described in man by M J Purdy (Hamilton)

Man 51 a stock auctioneer who often handled sheep suffering

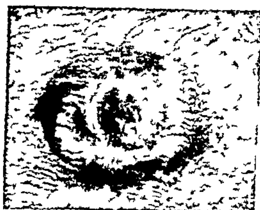


Fig 16—L on o ba k of h d I day ft et (Co t y of P dy M J New Zealand M J 54 572 575 O t be 1955)

from scabby mouth presented with a turbid bulla on the dorsum of his right hand The 1 cm lesion had a crusted center and contained little fluid Two days later it was over 1 in in diameter was raised and full of blood and had a central hemispherical dome covered with white sodden skin Two days later still the white covering over the dome had disappeared leaving a red shiny surface (Fig 16)

Usually a skin abrasion is necessary for human infection commonly caused by the teeth of infected animals but also by

( ) New Zealand M J 54 57 575 October 1955

fences and thorny material buried in clothing The incubation period in man ranges from three to seven days The lesions may be single or multiple and are usually on exposed parts especially the upper limb and face The lesion is first a dark red papule but in a few days it becomes larger umbilicated and covered with sodden looking skin

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(3) M P oc. 2 9 14 J u ry 1956

taneous sensory loss may be severe and widespread involving light touch pain vibration position sense or only one of these Tendon reflexes often lost or diminished may be normal Tenderness in affected muscles may be severe particularly in larger muscle groups of the shoulder girdle and subcostal group and may present with fibrillation Cerebrospinal fluid is usually normal but occasionally the globulin is increased Relapses are frequent and an apparently short lived illness has often become protracted and distressing

* [*This appears to be similar to the disease described in the succeeding article and to that reported in other parts of the world as Iceland disease Sigurdsson who described it in Iceland has recently suggested that it be called Akureyri disease (Lancet 1 766 May 26 1956)*—Ed]

Further Investigations on a Disease Resembling Poliomyelitis Seen in Adelaide in five patients are reported by R A A Pellew and J A R Miles[4] None had pleocytosis In the early stages the condition is indistinguishable from poliomyelitis The patients complained of bursting headache stiff back and neck aching limbs pain behind the eyes upper respiratory tract infection mild muscle weakness and a fever followed by lysis over three days Between the seventh and tenth days the temperature often rose and the symptoms recurred The limbs ached persistently and muscle weakness was mild Recovery eventually was good The worst sequelae were psychologic with symptoms of irritability depression lack of concentration and emotional instability

Laboratory investigations were unsuccessful in demonstrating the presence of a virus Paired serums for antibodies to three types of poliomyelitis virus mumps lymphocytic choriomeningitis encephalomyocarditis Port Augusta meningitis and leptospirosis showed that none of these agents was likely to have caused disease in all five patients

MISCELLANEOUS

Use of Morphine in Terminating Chills and as an Antipyretic Walter E Marchand[5] (V A Hosp Bedford Mass) reports a hitherto undescribed action of morphine i e its ability to terminate chills In his experience prompt and

(4) M J Australia 2 480-482 Sept. 24 1955
(5) New England J Med. 253 315 318 Aug 25 1955

comforting relief followed intravenous injection of 8 30 mg No adverse reactions were encountered

Calcium chloride has been reported to terminate chills but this therapy has several limitations Calcium chloride is potentially dangerous from a cardiac point of view it frequently causes phlebitis and marked tissue destruction occurs if it is infiltrated around the vein Intravenous administration of morphine is relatively free from danger unless used injudiciously

The antipyretic effect of morphine has been described in the literature This finding was confirmed and found to be useful clinically If morphine is given early in malarial paroxysm in a relatively large dose the chill can be prevented and fever suppressed

Significance of Diphtheroids in Malignant Disease Studied by Germ Free Technics Re evaluation in Hodgkin s Disease Lymphoma and Mouse Carcinoma was made by Robert Kassel and Antonio Rottino[6] (New York) because of the persistent isolation of a diphtheroid with acid fast properties in blood cultures from these sources In 31 patients with Hodgkin s disease or lymphosarcoma proved by biopsy a diphtheroid was isolated from 20% of the blood cultures The organisms appeared as coccoid bodies rods and club shaped forms the variation in shape apparently manifesting pleomorphism The bacteria were the same as those isolated by Fleisher

Since all sources of contamination had not been completely excluded a small germ free hood was used for further study Blood samples were obtained in the operating room after preparing the site of venipuncture with pHisohex for 15 minutes and draping with sterile towels The investigator scrubbed as for any operating room procedure wore sterile gown and gloves and withdrew 10 cc of blood into a silicone coated syringe which had been autoclaved with the needle attached Duplicate cultures were made one in the germ free hood and one in the sterile room Thirty subjects were used 19 patients with Hodgkin s disease 5 healthy controls 4 patients with leukemia 1 with lymphosarcoma and 1 with lung carcinoma

Of 57 cultures carried on in the germ free hood 57 were

(6) A M A A b I t M d 96 804 808 D mb 1955

taneous sensory loss may be severe and widespread involving light touch pain vibration position sense or only one of these Tendon reflexes often lost or diminished may be normal Tenderness in affected muscles may be severe particularly in larger muscle groups of the shoulder girdle and subcostal group and may present with fibrillation Cerebrospinal fluid is usually normal but occasionally the globulin is increased Relapses are frequent and an apparently short lived illness has often become protracted and distressing

• [This appears to be similar to the disease described in the succeeding article and to that reported in other parts of the world as Iceland disease Sigurdsson who described it in Iceland has recently suggested that it be called Akureyri disease (Lancet 1 766 May 26 1956) —Ed]

Further Investigations on a Disease Resembling Poliomyelitis Seen in Adelaide in five patients are reported by R A A Pellew and J A R Miles[4] None had pleocytosis In the early stages the condition is indistinguishable from poliomyelitis The patients complained of bursting headache stiff back and neck aching limbs pain behind the eyes upper respiratory tract infection mild muscle weakness and a fever followed by lysis over three days Between the seventh and tenth days the temperature often rose and the symptoms recurred The limbs ached persistently and muscle weakness was mild Recovery eventually was good The worst sequelae were psychologic with symptoms of irritability depression lack of concentration and emotional instability

Laboratory investigations were unsuccessful in demonstrating the presence of a virus Paired serums for antibodies to three types of poliomyelitis virus mumps lymphocytic choriomeningitis encephalomyocarditis Port Augusta meningitis and leptospirosis showed that none of these agents was likely to have caused disease in all five patients

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MISCELLANEOUS

Use of Morphine in Terminating Chills and as an Antipyretic Walter E Marchand[5] (V A Hosp Bedford Mass) reports a hitherto undescribed action of morphine i e its ability to terminate chills In his experience prompt and

(4) M J Australia 430-45 Sept. 24 1955
(5) New England J Med. 253 315 318 Aug 25 1955

still present cramping recurred and was not relieved by calcium and morphine Hydrocortone intravenously and cortisone orally were ineffective

Intramuscular injection of 2 5 cc black widow spider antiserum provided marked symptomatic improvement within 1½ hours and he was completely asymptomatic by the next day

• [The clinical picture is indeed a dramatic one Most black widow spider bites are sustained while using outdoor toilets and are especially likely to occur on the male genitalia —Ed]

Vaccinia vs Poliomyelitis? D P MacIver[8] found an inverse relation between vaccination against smallpox and occurrence of paralytic poliomyelitis in young children Between 1946 and 1955 in a mainly urban area with a population of 87 000 where a small majority of children are vaccinated in infancy 21 unvaccinated children under age 5 had paralytic poliomyelitis but it developed in only 4 comparable vaccinated children Of the 19 children under age 3½ who contracted poliomyelitis 17 had never been vaccinated and 1 had been vaccinated only four days previously

Poliomyelitis occurred equally in vaccinated and unvaccinated school aged children Evidently smallpox vaccination in infancy does not alter incidence of poliomyelitis in the age group 5 15 Among the younger children constituting 25% of the cases of poliomyelitis vaccination is apparently important Social and geographic factors were noncontributory

• [The figures are impressive and the lead is deserving of further study —Ed]

(8) La et 1 226 28 F b 4 1956

negative on blood plates and/or blood slants after two weeks incubation Of 48 duplicate samples in the sterile room 4 were positive for the diphtheroid organisms

These experiments do not conclusively prove that Hodgkin s disease is not caused by a blood borne organism but they emphasize the extreme sterile technic necessary to exclude unusual contaminants The results clearly indicate that the organism arose from a source other than the original blood sample Rigorous sterile technic is mandatory in dealing with cultures from patients with diseases of unknown etiology

• [This is a valuable contribution since reports appear from time to time stating that bacteria may be demonstrated in blood cultures of patients with lymphoma etc after prolonged incubation The present work provides sound evidence that almost unavoidable contamination by slow growing diphtheroids (from the air etc ?) may be responsible —Ed]

Black Widow Spider Poisoning is described and a case report and brief review of therapy are presented by Barrett L Taussig and Aaron Hendin[7] (St Louis) The signs and symptoms are characteristic although possibly confusing if a history of the bite is not obtained From 15 minutes to 2 hours after the bite severe muscular pain usually begins in the groin and spreads over the entire body The pain is excruciating and may exceed that of ruptured viscus or kidney colic often most severe in the abdomen and back The most striking physical findings include the obvious agony of the patient his inability to sit still or lie down and the extreme rigidity of the abdomen without tenderness to palpation The acute symptoms usually subside in 6 48 hours but may persist for several days

Opiates and analgesics are ineffective in relieving the symptoms Calcium salts intravenously neostigmine methylsulfate curare like drugs cortisone and ACTH have all been used The best and only specific treatment is the use of antivenin (Latrodectus mactans) in doses of 2 5 cc in deep intramuscular injection Some patients require an additional dose

Man 28 felt a sting on his right wrist and 15 minutes later had cramping in his chest arms and legs Two hours later he had spasm of all his muscles and rigidity of abdominal muscles Benadryl® intravenously was ineffective but calcium gluconate and morphine gave some relief The following morning the boardlike rigidity was

(7) Missouri Med 52 714 September 1955

The Chest



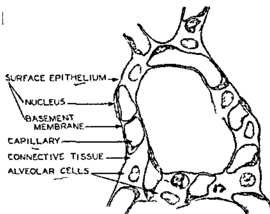
CARL MUSCHENHEIM M D

PART II

THE CHEST

ANATOMY

Structure of Respiratory Tissue was studied histochemically by L. D. Bertalanffy and C. P. Leblond.[1] The respiratory tissue of the lung—the alveolar wall—is composed of cells, capillaries and interstitial connective tissue. Three main concepts of alveolar wall lining have been (1) non



Fg 17 S f p th l m on pt (C rt y f B rt l ffy F D d L bl d C P L t 2 1365 1368 D 31 1955)

nucleated plates, (2) bare alveolus and (3) simple squamous epithelium. Until recently no decisive evidence was available for any of the theories, but histochemistry and the electron microscope provide evidence supporting the concept of simple squamous epithelium (Fig. 17).

The alveolar walls are lined by two juxtaposed structures

(1) La t 2 1365 1368 Dec 31 1955

Maximum inspiratory flow rates were 3-4 L/second Expiratory flow rates reached maxima of 5 6 5 L/second The changes in pressure and flow during cough are shown in Figure 18 The projected outlines of the trachea and main bronchi in Figure 19 are correlated and indicated by the dotted line in Figure 18

A transwall pressure gradient of 40 cm H O reduced the

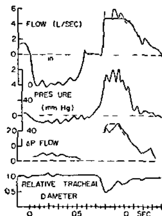


Fig 18—M m t t k d g b d th p ec d g p t on f h lthy m T p t bott m l m flow f phageal p t t fl w (Δ P/flow) d l t w dth f t ach l h d w (pp t d m t) h ta ed f m fl phic film (C rt y f B B R t l J Appl Phy l 8 264-268 Nov mb 1955)

cross section area to about one fifth its original size volume flow rates and linear velocities were markedly accelerated A mechanical cough apparatus produces a relatively small pressure gradient and a low flow rate with low linear velocities

The physical mechanism of cough involves combined high intrapleural pressure on expiratory volume flow rate and lung airway diameters creating a high linear velocity air stream with a high kinetic energy available for the acceleration and displacement of an object in the airway Reduction in lumen size differentiates a cough from a forceful expiration These diameter changes are induced by glottal clo

a squamous epithelium and its basement membrane When the classic theories were re examined it was apparent that the nuclei which are part of the surface epithelium were considered by supporters of the bare alveolus theory to belong to the capillary endothelium The non nucleated plates previously described by silver impregnation may be the cytoplasm of the epithelial cells as silver impregnation may outline these cells without demonstrating the nuclei

The cells in alveolar walls consist of simple squamous epithelium and simple squamous endothelium of the capillaries formerly referred to as endothelium like cells and together constitute 56% of all nuclei in the respiratory tissue of the rat Leukocytes comprise 13% of the cells present the other 31% being alveolar cells which are phagocytic and motile

The concept presented here is that alveolar tissue is lined by epithelium composed of extremely attenuated squamous cells resting on a basement membrane and that the alveolar cells within the walls are connective tissue cells at various degrees of differentiation This conforms with the classic tenets of histology since it implies the association of an epithelium with an underlying connective tissue stroma

• [These histochemical studies of Drs Bertalanffy and Leblond support the electron microscopic findings of Low (Anat Rec 117 251 19 3) which indicate that there is an alveolar epithelium For a comprehensive review of Current Concepts of the Finer Structure of the Lung see Krahl A M A Arch Int Med 96 342 1955—Ed]

PHYSIOLOGY

Physical Dynamics of Cough Mechanism By visualizing the trachea with high speed x ray motion pictures of the chest, B B Ross K Gramiak and H Kahn[2] (Univ of Rochester) recorded the changes in intrapleural pressure and rate of air flow during a cough Changes in the apparent diameter of the trachea were synchronous with changes in intrapleural pressure once the glottis opened and expiratory flow was started No wavelike diameter changes were found along the bronchial tree

(2) J Appl Phy 1 8 64 6 N embe 1955

when exercising J Butler and W Melville Arnott [a] (Birmingham England) estimated the effect of such alterations on the work of lung movement

Five normal men aged 24 36 were tested sitting upright a constant tidal volume of 500 ml was breathed at a fixed rate of 50 breaths/minute One subject was retested at varying respiratory rates Pressure volume recordings were

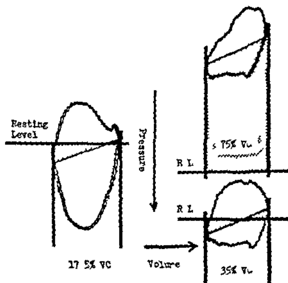


Fig 20—Res tory loop at d ff ent ent l tory l ls n on subject (C rtesy I B tle J a d Arnott W M Clin Sc 14 703 710 Novembe 1955)

made directly on photographic film by a mechano-optical system connected to an intraesophageal tube The movement of the reflected beam has a vertical component proportional to volume change and a horizontal component proportional to pressure change

Three vital capacity breaths were recorded after which resting esophageal and atmospheric pressures were measured After the subject exhaled completely and the end expiratory level was recorded he breathed in time with a met

(2a) Clin Sc 14 703-710 November 1955

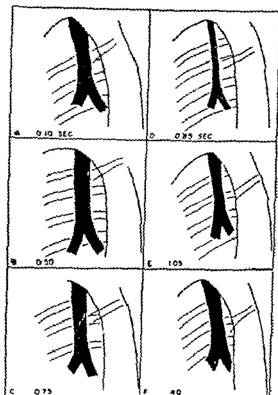


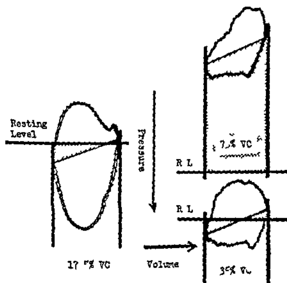
Fig 19—Tra i g f x y h d w f t achea befo d d g ough Time p nd to ent f Figu 18 w f m j ft nte obl q po t n (C f B D R J Appl Phy ol 8 264 268 N vembe 1955)

sure preceding the expiratory phase of the cough This permits the generation of a high initial expiratory pressure and once the glottis is opened a high pressure gradient across the walls of the trachea and bronchi of the lung

Work of Pulmonary Ventilation at Different Respiratory Levels At a constant respiratory rate the work of pulmonary ventilation during a single breath becomes greater with increase of tidal volume At a constant tidal volume the work increases with increased respiratory rate With a fixed volume and rate work is greater when the subject is supine than when erect and greater when he is at rest than

when exercising J Butler and W Melville Arnott (Birmingham England) estimated the effect of such alterations on the work of lung movement

Five normal men aged 24 36 were tested sitting upright a constant tidal volume of 500 ml was breathed at a fixed rate of 30 breaths/minute One subject was retested at varying respiratory rates Pressure volume recordings were



F g 20 —R to loop at d ff ent en lato y lev l on ubject (Cou t y f B tl J nd Arnott W M Cl n 14 703 710 Nov mber 1955)

made directly on photographic film by a mechano optical system connected to an intraesophageal tube The movement of the reflected beam has a vertical component proportional to volume change and a horizontal component proportional to pressure change

Three vital capacity breaths were recorded after which resting e ophageal and atmospheric pressures were measured After the subject exhaled completely and the end expiratory level was recorded he breathed in time with a met

(2) Cl Sc 14 703 710 N ember 1955

ronome within a 500 ml range and the resting esophageal and atmospheric pressures were again recorded (Fig 20)

The work of a complete respiration overcomes both elastic and viscous forces Viscous work is done in moving air and in deforming tissues and is represented by the area within the loop in a complete respiration

When the subject is breathing normally and returning to

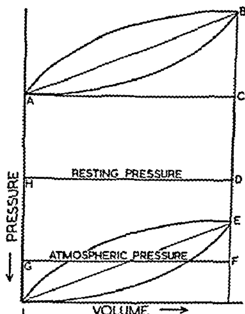
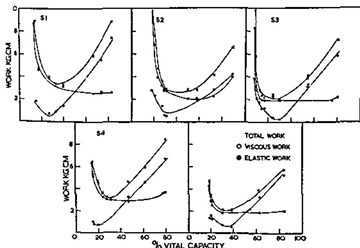


Fig 21 [illegible] (Courtesy [illegible] Clin [illegible] 14 703 710 November 1955)

the resting pressure at the end of each breath all elastic work is done in inspiration represented by the right angled triangle when the hypotenuse joins the elastic pressure recorded at moments of phase reversal The breaths at higher respiratory levels are performed at more negative pressures necessitating elastic work to accommodate the tidal volume and also effort *from the respiratory muscles to sustain* initial tension during the volume change The total inspiratory elastic work done were the lungs free in the atmosphere

would be equivalent to quadrilateral *ABFG* with atmos pheric pressure as the base line (Fig 21) The relaxed chest wall however maintains a force on the lungs thus cancel ing the work represented by area *HDFG* and leaving only area *ABDH* which represents the total elastic work of such an inspiration At levels below the resting respiratory level



F g 2 —W k f gl b th t d ff t p t y l l h m l b bj t (C t y f B tl J d A ott W M Cl S 14 0 710 N m b 1955)

pressures are positive relative to resting pressure and elas tic work is done in expiration represented by area *HDEI*

Results in the five men are shown in Figure 22 Individual data were strikingly similar The total work of lung ventila tion varied greatly at different respiratory levels Below the normal respiratory level the work increases mainly as a re sult of an increase in the viscous component Above this level the increase is due to an increase in the elastic work necessary Within the functional residual volume expiratory viscous work is greater than inspiratory The work of pul monary ventilation is minimal at about the normal resting respiratory level

ronome within a 500 ml range and the resting esophageal and atmospheric pressures were again recorded (Fig 20)

The work of a complete respiration overcomes both elastic and viscous forces Viscous work is done in moving air and in deforming tissues and is represented by the area within the loop in a complete respiration

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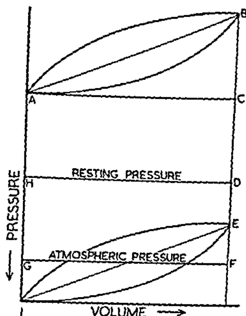
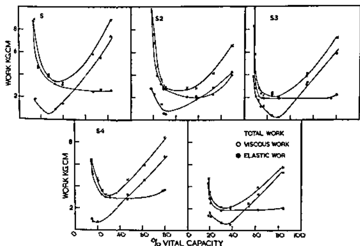


Fig 2—Pr e lum ec d g (Co t y f B d J d A n d W M Cl Sc 24 03 710 November 1955)

the resting pressure at the end of each breath all elastic work is done in inspiration represented by the right angled triangle when the hypotenuse joins the elastic pressures recorded at moments of phase reversal The breaths at higher respiratory levels are performed at more negative pressures necessitating elastic work to accommodate the tidal volume and also effort from the respiratory muscles to sustain initial tension during the volume change The total inspiratory elastic work done were the lungs free in the atmosphere

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Fg 22—W k f gl b th t d ff t p t y l l fi m l bj t (C t y f B tler J d A tt W M Cl S 14 703 710 N m b 19 5)

pressures are positive relative to re ting pressure and elastic work is done in expiration represented by area *HDEI*

Results in the five men are shown in Figure 22 Individual data were strikingly similar The total work of lung ventilation varied greatly at different respiratory levels Below the normal respiratory level the work increases mainly as a result of an increase in the viscous component Above this level the increase is due to an increase in the elastic work necessary Within the functional residual volume expiratory viscous work is greater than inspiratory The work of pulmonary ventilation is minimal at about the normal resting respiratory level

Mechanical Properties of Lungs in Emphysema are described by J Mead I Lindgren and E A Gaensler[3] (Harvard Univ) who studied 10 individuals with advanced pulmonary emphysema and for comparison, 10 normal persons Figure 23 a typical tracing of an emphysematous pa

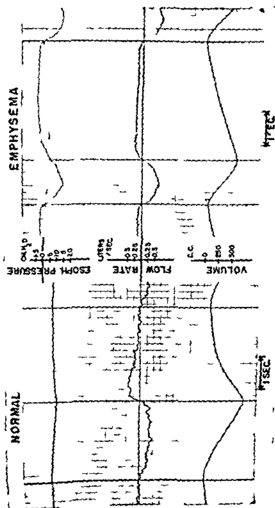
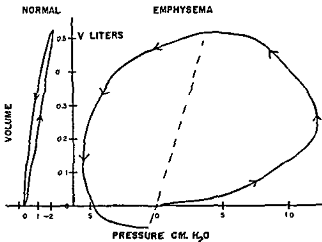
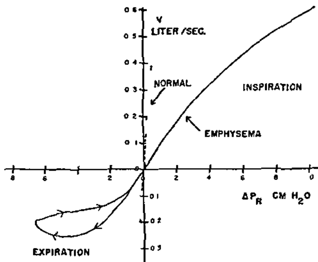


Fig 23—Typical tracings during quiet breathing in normal subject and patient with pulmonary emphysema Dotted line on pressure tracing on right represents calculated elastic component of pressure change (Courtesy of Mead J *et al* J Clin Invest 34 (pt 1) 1005 1016 July 1955)

(3) J Clin Invest 34 (pt 1) 1005 1016 July 1955





F g 24 (t p) —P v lum graph f m wh h p lmon ry mpl may be m d.
F g 25 (bottom) —R t p e fl w g ph f om wh ch p lmon ry flow ta ce m y be m d
Court y f Mead J t I J Cl I est 34 (pt 1) 1005 1016 J ly 1955)

tient during quiet breathing with a similar tracing of a normal person, shows that the breathing patterns in emphysema differ strikingly from the normal although tidal volumes and breathing frequencies are nearly the same Prolonged expirations and obliteration of coarse irregularities in the flow patterns were seen in all patients studied Pressure volume tracings for the cycles in Figures 23 show that compliance of the lungs is about the same in the two

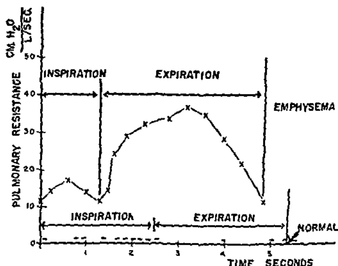


Fig 26—Pulm y fl w e t ce h ge du i g e i rat ry cycle (C rte y of M ad J t al J Clin I e t 34 (pt 1) 1005 1016 J ly 1955)

subjects (Fig 24) The fatness of the loop is much greater in the patient with emphysema due to the increased resistance this is shown more clearly in Figure 25 in which the flow resistive pressure difference is on the abscissa and rate of flow on the ordinate In this graph inspiration and expiration both start and end at the origin During inspiration the relation of flow to pressure is the same for increasing and decreasing phases of flow rate resulting in single curved lines *This is also true of the normal but the patient s* expiration describes a loop Early in expiration the patient has a flow of 0 2 L /second at a cost of a little more than 2

cm of water pressure Later the same flow costs more than three times this pressure This increase in expiratory resistance is plotted against time (Fig 26) Pulmonary flow resistance in the emphysematous patient is much greater than normal and during expiration becomes 50 times as great Pulmonary flow resistance during expiration is further increased by increased effort

In the patients with emphysema pulmonary compliance was near normal levels during quiet breathing but fell markedly as breathing frequency was increased

Pulmonary emphysema with its irreversible structural damage must be differentiated from bronchial asthma *which is reversible The two conditions have similar pul*monary mechanics increases in pulmonary flow resistance are greatest during expiration and pulmonary compliance falls with increased rates of breathing Theoretically certain mechanical differences should be measurable The static compliance of the lungs in emphysema should be higher than normal Furthermore the patient with asthma when relatively free from attacks should show little change in compliance with frequency and near normal pulmonary flow resistance The patient with emphysema in similar circumstances would still show marked mechanical abnormality

Clinical and Physiologic Aspects of Case of Obesity Polycythemia and Alveolar Hypoventilation is reported by J Howland Auchincloss Jr Ellen Cook and Attilio D Renzetti[4] (State Univ of New York Syracuse)

Man 30 had weighed over 200 lb for 13 years and had had frequent respiratory infections and nonproductive cough for 4 years and elevated hematocrit values progressive dyspnea and ankle edema for about 2 years which had prevented work On hospitalization he was alert cyanotic orthopneic weighed 290 lb and was 67 in tall He had *a few rales at the right posterior base gallop rhythm* accentuated second pulmonic sound mild edema of the abdominal wall and marked edema of the lower extremities Hemoglobin and hematocrit values and red blood cell count were elevated and bone marrow was hyperplastic in the erythroid series Chest x ray showed cardiac enlargement and enlargement of pulmonary vessels An ECG showed right ventricular hypertrophy Treatment consisted of bed rest digitalis sodium and caloric restriction mercurials and repeated phlebotomies He lost 54 lb during the month of hospitalization and became

(4) J Cl I t 34 1537 1545 O t b 1955

free from dyspnea and edema and less cyanotic Repeat che t x ray showed diminished vascular markings

Physiologic studies revealed reduced vital and total lung capacity and normal maximal ventilatory capacity Obstructive emphysema was not present Total minute ventilation was normal but tidal volume was reduced Arterial oxygen tension and oxyhemoglobin per cent saturation were extremely low and carbon dioxide tension greatly increased Inhalation of oxygen further reduced tidal volume and increased arterial blood carbon dioxide tension but raised arterial oxygen saturation only to 89% Physiologic dead space and diffusing capacity of the lung were normal at rest but percentage of venous admixture was greatly increased Right ventricular end diastolic and pulmonary artery pressures were increased

After removal of 5 L blood during 17 days total blood volume and red cell mass became normal Sodium and caloric restriction were maintained and digitalis continued for 10 months Repeat studies showed no changes in lung volumes or ventilatory capacity Erythrocytosis did not recur Tidal volume progressively increased and arterial oxygen and carbon dioxide tensions returned toward normal Alveolar ventilation could be improved by inspiratory po itive pres ure breathing Maximal diffusing capacity became normal Repeat cardiac catheterization revealed lower but still elevated pulmonary artery and end diastolic right ventricular pressures No evidence of abnormal cardiac or vascular communication was noted

All physiologic abnormalities were attributed to alveolar hypoventilation The small tidal volume probably left areas of lung in which blood circulation was maintained without adequate ventilation leading to an increased venous admixture Hypoxia over long periods may lead to polycythemia which then may lead to pulmonary hypertension and right heart failure An initiating mechanism for the alveolar hypoventilation was not found Obesity by increasing the mechanical work of breathing or conceivably by reflex effects may possibly have caused decreased tidal volume

• [This case bears similarities to a category of which several examples have been reported of severe arterial hypoxia with polycythemia in the absence of associated primary lung disease or of abnormal cardiac or vascular communications It has been postulated that these may be cases of polycythemia vera with some unexplained effect on the lung or on the respiratory center or contrariwise that the polycythemia is secondary to a primary respiratory center disease of unknown etiology Obesity which may have been a factor in this case was not present in other cases The physiologic abnormalities observed are not those characterist c of primary pulmonary vascular disease but in the present instance this could not be ruled out —Ed]

Respiratory and Renal Effects of a Carbonic Anhydrase Inhibitor (Diamox®) on Acid Base Balance in Normal Man and Patients with Respiratory Acidosis *Morton Galdston* (New York Univ) studied the immediate and long term effects of 2 2 6 3 mg /kg diamox® every six hours in terms of acid base balance plasma electrolytes urinary electrolyte excretion and respiratory and metabolic rates in five patients with chronic lung disease and respiratory acidosis and in five without lung heart or kidney disease

Within four hours of a single dose the plasma bicarbonate level fell in all the patients urine became alkaline and diuresis of sodium potassium and bicarbonate ions commenced Arterial Pco and pH were not consistently changed The intensity of the changes was unrelated to the dose of diamox® or the initial levels of plasma constituents

After the first few days in all but one patient the urine was no longer alkaline and diuresis of sodium potassium and bicarbonate ceased Prolonged administration significantly reduced the plasma bicarbonate level Arterial Pco fell significantly in three and arterial pH in two patients without heart lung or kidney disease A significant decrease in arterial Pco was seen in two patients with emphysema and one became more acidotic Arterial pH did not rise to normal levels in the patients with emphysema or to control levels in the patients without heart lung or kidney disease

Hyperventilation or increased tidal air and moderate slowing of respiration while minute volume of respiration remained relatively unchanged accounted for instances of sustained decrease in arterial Pco ri e in aveolar Po and alveolar ventilation

Ventilatory adjustments to prolonged use of diamox® apparently involve stimuli other than those of Gray s multiple chemical factor theory of the regulation of ventilation

In chronic emphysema patients diamox® intensified the

(5) Am J M d. 19 516-532 Oct be 1955

acidosis by reducing the plasma bicarbonate but did not alter respiratory depression during inhalation of 100% O

In some patients with chronic respiratory acidosis the administration of diamox® every six hours is disadvantageous because the acidosis is intensified when the plasma bicarbonate is depleted After discontinuing the drug several days are required before the bicarbonate levels return to control levels

● [This study similarly to several earlier studies (see 1955 56 YEAR BOOK pp 129 134) *indicates that the effects of diamox® on respiration* and acid base balance are complex and perhaps not always beneficial in respiratory acidosis The inconsistency observed in the changes of arterial blood Pco *and the apparent intensification of the respiratory acidosis* in some patients is disturbing if this drug is to be used widely in emphysema with CO retention Fishman *et al* (see next article) however have observed a more consistently favorable trend toward reduction of Pco in their patients who received the total daily dose of diamox® undivided and whose blood samples were usually drawn not within a few hours of receiving the drug when the metabolic acidosis is at its height but after 24 hours when the arterial blood pH has returned to relatively normal The prolonged administration of diamox® in a single daily dose in contrast to divided doses also seems to result more consistently in favorable symptomatic effects in patients with chronic CO retention (see Fishman *et al* next article) —Ed]

Ventilatory Drive in Chronic Pulmonary Emphysema A P Fishman P Samet and André Cournand[6] (Columbia Univ) studied 42 patients in four classifications (1) with emphysema and CO retention (2) with emphysema but without CO retention (3) cardiac or pulmonary disease without emphysema and (4) control patients *without* cardiac or pulmonary disease Some patients with chronic pulmonary emphysema manifest an abnormally small increase in minute ventilation when CO_2 is added to inspired air This response despite a considerable increase in arterial blood CO_2 tension (Pco) is characteristic of patients with chronic pulmonary emphysema and chronic CO_2 retention

The mechanism of this *abnormal ventilatory response* seems to be selective depression of the respiratory center to the stimulus of increased arterial Pco and/or hydrogen ion concentration since responsiveness to stimuli such as exercise is maintained

The poor ventilatory response to CO stimulus is generally not reversible in patients with CO_2 retention *of long* duration even though *arterial blood Pco* and alkali reserve

(6) Am J M d 19 533 548 O t be 1955

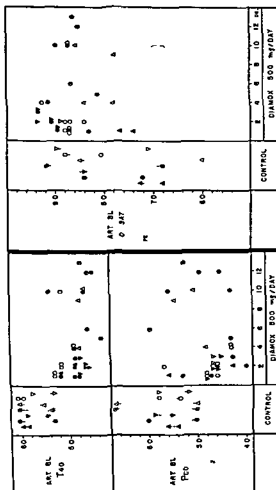
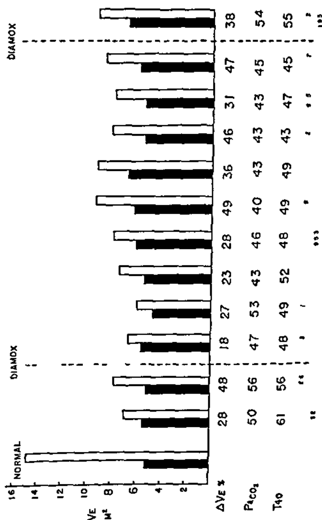


Fig 27—Effect of d ... th ... py ... CO ... indicated by broken ... symbols ... P ... *et al* Am J Med 19 533 548 October 1955)

can be restored toward normal levels by prolonged administration of the carbonic anhydrase inhibitor diamox® Seven patients with emphysema and CO retention received 500 mg diamox® daily for one year Figure 27 shows changes in the alkali reserve (T_{40}) arterial blood Pco and oxyhemoglobin saturation Arterial blood Pco_2 and T_{40} decreased



F g 28 —I fl c f rt l blood Pco and alkal on ng nd aft r d m x® th apy S l d block p nt th m ut v t l t y p nse block p e t th m t t l t on wh l b th g 5% CO t l t n wl l l th g pat nt bef du w th n th tw b k n t l l n (C t y f F h n A P d t olt n d d g d h t th p n 1955) t l Am J Med 19 533 548 O t be

during diamox® treatment but Pco levels fluctuated with a tendency to reduction Of the seven patients five had no change in ventilatory response to 5% CO_2 in air before or during diamox® therapy and in only two was the response somewhat greater during diamox® therapy than before (Fig 28) Even in these two patients the increased response

remained substantially less than in either control subjects or patients with emphysema without CO_2 retention

The relief or aggravation of hypoxemia within the physiologic range has little effect on the ventilatory response to inspired CO_2 in patients with emphysema and CO_2 retention The hypoxic stimulus probably is weak however breathing pure O_2 consistently depresses the ventilatory response

The noxious effects of CO_2 retention may be considered physical physiologic and pharmacologic Physically an elevated alveolar CO_2 tension has a reciprocal effect on alveolar O_2 tension The adverse physiologic effect on the respiratory center once established is not reversible Restoring the CO_2 content and partial pressure of CO_2 to normal limits is difficult because the body tissue reservoir of CO_2 is enormous and its regulation depends on kidney reabsorption of bicarbonate and other cations and available tissue buffer base as well as pulmonary function A high arterial P_{CO_2} is an essential stimulus leading to augmented alkali reserve by the kidney The mechanism of diamox® in reducing alkali reserve is clear but the concomitant reduction in arterial P_{CO_2} is unexplained

The pharmacologic effect of increased CO_2 tensions is depression of the central nervous system to the point of anesthesia Patients with emphysema and CO_2 retention who have been treated with high concentrations of O_2 may become mentally depressed somnolent and even comatose This is generally ascribed to increased CO_2 retention subsequent to a suppressed hypoxic stimulus Clinically however the patient with emphysema and CO_2 retention untreated is drowsy apathetic and mentally sluggish Diamox® has restored mental alertness and vitality to these patients

Carbon dioxide retention can be prevented and controlled by improved alveolar ventilation and bicarbonate elimination by the kidney Alveolar ventilation can be improved by breathing exercises bronchodilators reduced pulmonary blood volume and mechanical regulation of ventilation The best current method for promoting bicarbonate excretion by the kidney is the use of carbonic anhydrase inhibitors which promote excretion of bicarbonate and bicarbonate

	NORMAL			DIAMOX									DIAMOX
ΔVE %		28	48	18	27	23	28	49	36	46	31	47	38
P_{ACO_2}		50	56	47	53	43	46	40	43	43	43	45	54
T40		61	56	48	49	52	48	49	49	43	47	45	55

Fig 28—[illegible] blood Pco [illegible] Sod block [illegible] 5% CO [illegible] 1955)

during diamox® treatment but Pco levels fluctuated with a tendency to reduction Of the seven patients five had no change in ventilatory response to 5% CO in air before or during diamox® therapy and in only two was the response somewhat greater during diamox® therapy than before (Fig 28) Even in these two patients the increased response

chronic pulmonary emphysema anoxemia and hypercapnia 6 8 Gm sodium salicylate given intravenously over about an hour lowered the arterial Pco raised arterial blood pH and increased arterial blood oxygen saturation When oxygen inhalation aggravated the hypercapnia 6 8 Gm sodium salicylate intravenously reduced the hypercapnia Aspirin 3 7 Gm daily in divided doses for a few days produced variable results Hypercapnia was reduced in some patients by relatively low plasma salicylate levels in others by only rather high levels and in others was not reduced by any level

Salicylates stimulate the respiratory center in animals and man but the exact site of stimulation is unknown In normal animals and man and in patients with emphysema and CO retention salicylates lower the arterial Pco and raise arterial pH Hyperventilation was observed in the patients after intravenous injections of salicylates and the immediate effects of salicylate on the acid base equilibrium could be explained by increased pulmonary ventilation

Salicylates may prove useful as relatively long acting respiratory stimulants but further experiments are necessary They may also be useful as an adjunct in the treatment of pulmonary emphysema when concurrent severe anoxemia and hypercapnia make oxygen administration necessary although hazardous

Relief of Carbon Dioxide Narcosis by Simple Intermittent Positive Pressure Therapy is described by Theodore H Noehren[8] (Buffalo) In patients with long standing hypoxia particularly due to pulmonary emphysema carbon dioxide tension progressively increases in alveolar air and blood and the respiratory center gradually loses its sensitivity to carbon dioxide Other centers the chemoreceptors of the aortic and carotid bodies then control respiration with hypoxia as the stimulus Oxygen therapy is often urgent in patients with extreme cyanosis but in the patient with hypercapnia and acidosis the relief of hypoxia even further depresses respiration Delirium mania coma and even death may ensue The prime need in such patients is elimination of carbon dioxide by hyperventilation to restore respiratory center *sensitivity*

(8) D Ch t 28 515 5 N mbe 1955

bound base by the kidney apparently by interfering with the hydrogen ion exchange mechanisms for sodium This may also influence CO_2 excretion but the amounts excreted in the urine are probably insignificant The weak diuretic effect of diamox® may indirectly augment alveolar ventilation by decreasing the volume of blood in the lungs

For therapy of CO retention patients with chronic pulmonary emphysema may be divided into three groups (1) those without CO retention (2) those who tend to retain CO_2 either at rest or with exercise and (3) those with chronic CO retention Acute bronchitis or pulmonary infection may precipitate or aggravate respiratory acidosis in all three groups In the absence of acute respiratory infection the first group does not require mechanical hyperventilation or diamox® In the second group CO_2 retention should be prevented Mechanical ventilation for brief periods daily promotes CO_2 excretion and patients addicted to O_2 therapy may be benefited by mechanical hyperventilation Diamox® has not been established as useful in these patients In the third group mechanical hyperventilation and diamox® are indicated to deplete CO stores Diamox® is administered in one dose of 0 5 Gm daily indefinitely The return of arterial blood Pco toward normal and the reduction in alkali reserve may obviate the need for continued mechanical hyperventilation

Respiratory acidosis as indicated by arterial blood analysis demands prompt institution of mechanical hyperventilation and diamox® therapy to supplement the customary treatment with antibiotics for acute bronchitis or bronchopneumonia bronchodilators and specific measures for right sided heart failure if needed Mechanical hyperventilation is essential if O therapy is required to relieve hypoxemia In patients with chronic CO_2 retention diamox® therapy apart from its diuretic action facilitates clearing the sensorium and reduces the hazard of CO_2 narcosis

Effect of Salicylate on Acid Base Equilibrium of Patients with Chronic CO_2 Retention Due to Pulmonary Emphysema is reported by Rene Wegria Nicholas Capeci George Kiss Vincent V Glaviano John H Keating and James G Hilton[7] (St Luke s Hosp New York) In patients with

(7) Am J Med. 19 509 515 October 1955

chronic pulmonary emphysema anoxemia and hypercapnia 6 8 Gm sodium salicylate given intravenously over about an hour lowered the arterial Pco raised arterial blood pH and increased arterial blood oxygen saturation When oxygen inhalation aggravated the hypercapnia 6 8 Gm sodium salicylate intravenously reduced the hypercapnia Aspirin 3 7 Gm daily in divided doses for a few days produced variable results Hypercapnia was reduced in some patients by relatively low plasma salicylate levels in others by only rather high levels and in others was not reduced by any level

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(8) D Ch t 28 515 5 2 N mbe 1955

Man 57 had pulmonary disease for seven years and edema dysp *nea and weakness for three weeks* Temperature was *100 2 F* pulse 120 respirations 26 and blood pressure 148/88 He weighed 14) lb He was well oriented but drowsy mucous membranes were markedly cyanotic neck veins were distended chest cage expansion was lim ited wheezes and hyper resonance were present in the chest and the heart was enlarged He had marked edema

He was treated with aminophylline digitalis aerosol bronchodila tors diuretics penicillin chloramphenicol and a low salt diet Oxygen *therapy induced periods of irrationality and distress After a week of*

Clinical and Laboratory Data in Relation to Intermittent Positive Pressure Therapy*

R C rd Rea m Thru hou	Ca rol		IPPB I with Com Ai 12 m /H O							P tlow L			
D	1		9-	10	11	12	13	14	15-6	1	3		26
W ght lb	143	136		136	138	133	133	134		133	130	136	134
Temperatu	100	101		99	99	101	99	99		98	98		
pCO mm Hg (Norm 1 40)		63		49	4	47	46	47		4	44	47	38
O Per Cent S t. (Normal 90 <)		63		94	86	9	86	97		96	91	90	9
pH (N rm 1 7 4)		7 36		7.38	7 43	7.33	7 35	7.31		7.38	7.39	7.38	7 49
Hgb (N rm 1 14 6)		15 5		15 7	17 5	16 9	18 3	15 8		17..	16 4	16 6	14 0
V tal C pa ty Pred t d 3400 cc		1680			1957			2039		2018	1978	1590	1 64
M m m Breath ng Cap ty Pr d t d 93 L/m		15 7			30 9			36		38	30 6	34 1	31.5

Art al blood O nd CO co t t w nalyz d mmed tely by th m thod f V n Slyk d N ll The pCO wa d t m d f om the n mog am t S ger a d H ting and p lmonary fu ct on d t m ed n a Coll n p om t a d sc bed by B ldw C rnand a d R h d Th pH wa det m d by glass lectrod

this therapy he lost 13 lb of edema fluid but his general condition re mained unchanged Mechanical hyperventilation by intermittent pos itive pressure (IPPB/I) with compressed air was then added al most constantly the first three days and thereafter for several 10 minute periods daily During the first 24 hours he had 20 30 second periods of apnea and required constant nursing supervision

The table lists results of this procedure on the blood gases *Hyper* ventilation decreased the Pco from 63 to 49 mm. Hg and increased oxygen saturation from 63 to 94% Clinically the improvement was dramatic. Breathing increased in depth frequency and ease and col or improved He was more alert during the day and slept at night even sleeping with the positive pressure machine attached during the first three days

Compressed air activating the IPPB/I prevented the oxygen paradox usually encountered Even with compressed air short periods of apnea occur and may be serious Manual operation of the demand valve accommodates for this situation and respiration may be maintained if the inherent stimulus to respiration is lost

The dramatic and prolonged success of hyperventilation may be related to mechanical ventilation spontaneous hyperventilation cure of infection and relationship of carbon dioxide blood tension to pulmonary artery pressure Before IPPB/I therapy the patient was incapacitated despite adequate cardiac treatment Afterward his activity was markedly increased and he was maintained on the same cardiac regimen Positive pressure itself probably was not responsible Ventilation studies on a group of patients with emphysema before and after IPPB/I alone demonstrated no dramatic effects

Pulmonary hypertension from hypercapnia may be the controlling factor Correction of carbon dioxide retention may have lowered pulmonary artery pressure sufficiently to allow compensation of the failing right ventricle

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HAMMAN RICH SYNDROME

Diffuse Interstitial Pulmonary Fibrosis Henry L Wildberger and William R Barclay[9] (Univ of Chicago) report the Hamman Rich syndrome in two brothers

CASE 1—Man 52 could recall three episodes of left chest pain diagnosed as pleurisy and had been rejected for army service because of a chest x ray but was healthy until the year of hospitalization when dyspnea developed and rapidly progressed At no time did he have hemoptysis fever or night sweats His mother had died of bronchopneumonia and a brother at 38 of pulmonary fibrosis

He was a small emaciated white man dyspneic and cyanotic Blood pressure was 90/60 pulse 128 and respirations 48 The chest was hyper resonant and the diaphragm was limited in movement Coarse rales and rhonchi were heard The tuberculin skin test was positive at 1 1 000 and sedimentation rate was elevated In x ray he had multiple bilateral tiny densities often along the vascular pattern and sometimes coalescing into patchy infiltrates Vital capacity

(9) Ann I t. M d 43 11 7 1138 Novembe 1955

was 18% of predicted normal and maximal breathing capacity was reduced

Therapy with ACTH antibiotics potassium iodide theophylline and oxygen was without significant effect Deterioration was progressive and he died eight months after hospitalization

At autopsy the right ventricle was hypertrophied The lungs were uniformly firm and fibrous and did not collapse when the chest was opened Multiple fibrous septa formed nodules up to 1 cm in diameter some with calcified material Lymph nodes were enlarged Microscopically the lungs were diffusely infiltrated by fibrous tissue with varying amounts of collagen The alveoli were decreased in number and dilated with metaplasia of the lining cells Small island of bone were present

CASE 2—Man 38 brother of the first patient had dyspnea productive cough and weight loss for eight years Tuberculin test was positive in second strength Lung biopsy revealed generalized progressive interstitial infiltration During the last eight months of life his clinical condition progressively worsened despite oxygen antibiotics potassium iodide aminophylline and corticosteroids During ACTH therapy his appetite weight and morale improved temporarily

Autopsy findings were similar in the two cases grossly and microscopically

Characteristically the clinical course of diffuse interstitial pulmonary fibrosis is marked by an insidious onset and irremediable progression After symptoms begin survival may be weeks to years

Fibrosis of the lung is a nonspecific and general tissue reaction and numerous agents have been implicated in the etiology In many patients no cause can be demonstrated by current methods Genetic or constitutional predispositions may be factors involved

• [It is pointed out by Drs Wildberger and Barclay that the occurrence of the Hamman Rich syndrome in siblings has been reported before once in identical twin sisters who were geographically separated for 25 years before the onset of symptoms The present report like most others records the failure of steroid hormone therapy which in both patients effected no more than temporary symptomatic improvement In the second patient there occurred an acute exacerbation on reduction of ACTH dosage and there was failure to halt the deterioration with prompt restoration of even more than the original dose of ACTH plus cortisone This phenomenon was first noted by Peabody *et al* (see 1954 55 YEAR BOOK pp 200 202) The present authors question the interpretation that deterioration or sudden death in such instances is actually a consequence of the therapy They suggest that the coincidence of a dosage change with an inevitably fatal outcome may result merely from the fact that steroid hormone therapy is usually not given until the disease has reached its serious end stage

In the case reported by Drs Pinney and Harris (see next article) cortisone used in an earlier stage was beneficial and withdrawal of steroid administration was accomplished without exacerbation or relapse —Ed]

/Hamman Rich Syndrome Report of Case Diagnosed Ante morten by Lung Biopsy and Successfully Treated with Long Term Cortisone Therapy is presented by C T Pinney and H William Harris[1] (Fitzsimons Army Hosp)

Woman 27 was well until five months before hospitalization when cough mucoid sputum and dyspnea developed She lost 20 lb during the previous nine months Chest films at that time revealed bilateral widespread infiltration On her admission physical findings were normal and laboratory studies failed to disclose the cause of the infiltration A repeat chest film revealed extensive pulmonary infiltrates of a lacy and reticular appearance with fine and coarse nodularity and slight hilar lymphadenopathy A film taken three months before onset of symptoms had been entirely normal

At thoracotomy the lung appeared normal but felt granular Biopsy revealed severe diffuse interstitial fibrosis active in some areas with proliferation and relatively acellular in others Some alveoli were completely replaced others were lined with a hyaline type membrane and some contained hemorrhage and edema The inflammatory infiltrate was composed of lymphocytes moderate numbers of polymorphonuclear leukocytes and eosinophils Cultures smears and tissue stains were negative for acid fast bacilli fungi and bacteria

Two weeks later she was started on cortisone orally Within 48 hours improvement was noted in the cough and dyspnea On continued medication x rays showed improvement and eight months later were virtually normal She became asymptomatic and resumed relatively normal activities

The clinical diagnosi of Hamman Rich syndrome can be made only by excluding other chronic diseases causing diffuse pulmonary infiltration A proved diagnosis during life can be established only by biopsy Heretofore all reported therapy has been unsuccessful the cases perhaps being too far advanced Cortisone inhibits inflammatory exudates and granulation tissue but has little effect on mature fibrous tissue

Early recognition and prompt therapy are important if patients are to be benefited Relapses and death have occurred when treatment was stopped suggesting that the adrenal steroids suppress the host response to an unknown stimulus rather than removing the stimulus itself

• [In a similar personally observed case also diagnosed by lung biopsy in the stage before severe symptoms a like experience with respect to un

(1) Am J M d 0 308 313 F b y 1956

eventful withdrawal of cortisone may be mentioned In this instance how ever there was no appreciable improvement during therapy either symp tomatically or roentgenologically Lack of benefit may have been becau e of inadequate dosage (maximal daily cortisone 75 mg) or because the fibrosis was more mature Clinically and roentgenologically the disease was stable during therapy and it has continued without appreciable change subsequently The total observation period is nearly two years —Ed]

WEGENER S GRANULOMATOSIS (AND PERIARTERITIS NODOSA)

The grouping of the following three articles under the above heading may be questioned by some Indeed the use of the title Wegener s Granu lomatosis for necrotizing granulomatosis and angutis of the lungs and related pathology in other organs has been rejected by Fienberg (see 1954 55 YEAR BOOK pp 127 129) However the eponym appears to be gaining acceptance despite the recognized priority of Klinger and per haps it serves a purpose in bringing together descriptions of cases of great similarity and in differentiating them from periarteritis nodosa This differ entiation was actually first clearly made by Wegener Cases like those reported by Braunstein (p 135) which meet the histologic criteria of classic periarteritis are thus to be distinguished and are properly desig nated as pulmonary periarteritis nodosa There are in addition other forms of necrotizing pulmonary angutis to be distinguished from this syndrome The pathologic characteristics of Wegener s granulomatosis as stated in the first paragraph of the first article abstracted below are those formu lated by Fahey *et al* (Am J Med 17 168 1954) and by Godman and Churg (A M A Arch Path 58 533 1954) —Ed

Wegener s Granulomatosis *reported on by* E W Walton and P O Leggat[2] (Newcastle upon Tyne) is characterized by *necrotizing granulomas in the upper air passages* lower respiratory tract or both generalized focal necrotizing an gutis of arteries and veins in the lungs and other sites and glomerulitis with necrosis of loops of the capillary tuft cap sular adhesion and granulomas

Presenting symptoms may be sinusitis cough continued fever chest pain shortness of breath peripheral neuritis or deafness Both sexes are affected in all age groups most fre quently in the fourth and fifth decades Most patients have been in good health previously without asthma or allergy and have not had sulfonamide therapy Prognosis is uniform ly bad and death usually ensues in less than six months Possibly the pathogenesis is a lesion of unknown origin in

( ) J Clin Path 9 31 37 F b y 1956

the respiratory tract followed by a generalized hypersensitivity to bacterial or tissue breakdown products or to drug therapy

Woman, 42, had pleurisy which resolved on sulfonamide therapy. Chest x-rays showed homogenous shadows in the right middle and left lower lobes. Mantoux test was positive but tubercle bacilli could not be recovered from sputums or gastric washings. Lung biopsy was interpreted as indicating tuberculosis and streptomycin and PAS were given for three weeks. When these were discontinued, high fever and productive cough developed. Treatment was reinstituted but a sensitivity reaction occurred with fever, diffuse skin rash, eosinophilia, arthralgia and edema of the hands. Anosmia became marked and ulceration of the nasal septal mucosa was discovered which on biopsy was seen to be nonspecific granulation tissue. Attempted desensitization to streptomycin produced severe sensitivity reactions on two occasions, with polyarthritis, rash, peripheral neuritis, albuminuria, hematuria, cylindruria, episcleritis, buccal mucosa ulcerations and slight bilateral deafness. Anemia was severe. Pulmonary involvement progressed and she died.

Re-examination of the lung biopsy material revealed two nodular lesions of granulation tissue with many necrotic areas. Perinecrotic areas were avascular, infiltrated by polymorphonuclear leukocytes, plasma cells, lymphocytes and eosinophils. Giant cells, Langhans and foreign body type, were numerous. Arterioles near the granulomas showed endarteritis; internal elastic laminae were intact and there were no zones of fibrinoid degeneration. At necropsy the lung changes were similar to those in the biopsy material, but necrosis was more extensive. All glomeruli in the kidneys had focal fibrinoid necrosis of tuft loops, proliferation of tuft epithelium and frequent crescent formation. Many solitary granulomas were present in the spleen. Arteries and veins up to 0.5 cm. diameter in the spleen, kidney, pancreas, uterus, voluntary muscle and periadrenal adipose tissue showed fibrinoid necrosis of the wall, thrombosis and perivascular infiltration. Perivascular granulomas were frequent. In healed stages the occluded vessels were recanalized, fibrosis was perivascular and the media showed segmental fibrosis with loss of internal elastic lamina.

Roentgen Manifestations of Necrotizing Granulomatosis and Angiitis of the Lungs are presented by Daniel Kornblum and Robert Fienberg[3] (V. A. Hosp., Boston). A syndrome of granulomatosis with angiitis of the lungs, massive necrosis of the spleen and focal granulomatous glomerulonephritis has been reported with increasing frequency. Fienberg described two typical examples of this condition in 1953 [1954-55 YEAR BOOK, p. 127.—Ed.]. The roentgen findings in these

(3) Am. J. Roentgen. 74:587-59, Oct. 1955.

two cases and in a third case [Ibid p 128—Ed] in which the disease was limited to the lungs are described

CASE 1—Man 27 had hemoptysis weight loss night sweats and left chest pain for eight months Six years previously he had taken sulfonamides for one year to treat persistent cough and fever after pneumonia He had no history of allergy A cavity 3 cm diameter was seen on the initial chest film (Fig 29) in the posterior basal segment of the left lower lobe The lobe was excised Drenching sweats and fever arthritis gross hematuria albuminuria cylindruria

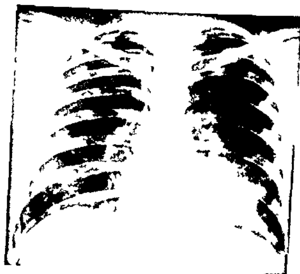


Fig 29—A f l dat n l ft l wer l be c nt g v t w th fl d l v l (Cou t y of K r bl m D d F e b g R Am. J Roentg l 74 587 592 O t ber 19 5)

epistaxes petechiae conjunctivitis and nodules in the lung fields developed He died two months later

CASE 2—Man 50 had dyspnea fever hemoptysis and occasional joint pains for a month There were signs of consolidation in both lung fields albuminuria hematuria cylindruria leukocytosis azotemia and blood sulfonamide level of 1 5 mg /100 ml Figure 30 shows the right lung by posteroanterior chest x ray Bilateral diffusely scattered discrete and confluent nodules up to 1 cm diameter not calcified were most prominent in the central portions Poorly demarcated densities obscured the hilar vessels No definite cavitation was seen He died nine days after hospitalization

CASE 3—Man 37 had hemoptysis for two days He had had episodes of night sweats dyspnea wheezing cough moderate spu

tum fatigue and sharp chest pains with occasional hemoptysis for two years He had rhonchi rales and wheezing in the right chest with diminished breath sounds Chest film showed a fairly well circumscribed mass 2 cm diameter in the anterior segment of the right upper lobe and a 4 cm mass in the anterior basal egment of the lower lobe (Fig 31) No calcium deposits or cavitations were seen



Fig 30—D ff p lm y d l t d t l d t gg t g d m (Cou t y f K Ll m D d F t g R Am J R tg l 74 587 59 O t b 19 5)

The parenchyma surrounding the lesions showed faint patchy con solidation with platelike atelectatic areas near the upper lobe lesion Multiple segmental lobectomies were performed and three masses removed He continued to have dyspnea wheezing and asthma 14 months postoperatively

The masses in the first two cases were granulomatous with little collagen Small foci of necrosis surrounded by epithelioid cells were numerous in the first case The bronchi

two cases and in a third case [Ibid p 128—Ed] in which the disease was limited to the lungs are described

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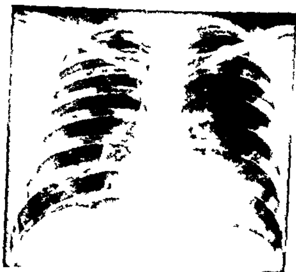


Fig 9—Ar of on l dat o n l ft lower l be conta g ca ty w th fl d l vel (Court sy f Ko nblum D and k e berg R Am. J Roe tg n l 74 587 59 Octobe 19 5)

epistaxes petechiae conjunctivitis and nodules in the lung fields developed He died two months later

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may be protracted but deterioration is usually rapid after onset of glomerulonephritis

Roentgen findings alone have never suggested the diagnosis since the distinguishing features are nonspecific Characteristically the lung lesions are nodular multiple up to several centimeters in diameter round discrete and fairly well demarcated The surrounding parenchymal consolidations may obscure the borders and when many lesions are present they may become confluent The nodules are not localized and calcium has not been seen Cavitation is a prominent x ray feature The cavities vary in size and may be multilocular with irregular walls The course of the lesions is variable from rapid progression to remaining stationary for years Focal atelectatic changes may be present near the nodules but no lobar contraction has been noted The heart is not enlarged and no pleural fluid has been seen

Periarteritis Nodosa Limited to Pulmonary Circulation Herbert Braunstein[4] (Ann Arbor Mich) described six cases of necrotizing angiitis in which the lesions were limited to the lungs and met the morphologic criteria for the diagnosis of periarteritis nodosa All the patients (five females and one boy aged 3½-47) had prolonged pulmonary hypertension

Three patients had advanced mitral stenosis one congenital absence of the interatrial septum one pulmonary hypertension of unknown etiology accompanied by pulmonary arterial and arteriolar sclerosis and one pulmonary hypertension associated with multiple miliary thrombotic occlusions of small pulmonary arteries The common association of pulmonary hypertension with this type of localized arteritis suggests a pathogenetic relationship

The lesions were limited to pulmonary arteries and were not associated with contiguous pneumonitis Pathologic changes were consistent with periarteritis nodosa described in the systemic form of the disea e in terms of histology size and type of vessels involved (small and medium sized arteries) acute and healing lesions present in the same patient and tendency for the changes to occur at points of bifurcation of arteries and to affect only part of the circumference of the involved vessels

(4) Am J P th 31 837 8 7 S pt O t 19

oles were ulcerated the walls destroyed and the lumens occluded Dilatation of these ulcerated structures led to cavity formation The walls of arteries and veins were replaced by fibroblasts, histiocytes and eosinophils with destruction of the elastic laminae Coagulative necrosis had occurred in the



Fig 31 —Left bl q w f le a t r r segme t f r ght pp l l and ma n a t r bas l gm nt of ght low l be h w ng fa t p t h s l dat i reg o f the m se d focal pl tel k t l tati cha g n v ty of upper odul (Cou t y of Ko nbl D a d F be g R Am J Roe tg l 74 587 592 Oct be 1955)

spleen and crescent formation glomerular thromboses and periglomerular granulomas in the kidney In the third case the lungs contained dense acellular fibrotic tissue with vacuolated macrophages with cholesterol rich lipid in the alve oli dilated bronchioles and metaplastic stratified squamous epithelium

Hemoptysis is common and fever night sweats joint pains weight loss and cough occur frequently Asthma may be present and eosinophilia is variable The clinical cour e

dust controls were generally adopted by the mining and manufacturing industries

The safe limit to dust with a free silica content of approximately 35% has been reported to be between 9 000 000 and 20 000 000 particles per cubic foot of air However as with other industrial hygiene standards this standard should be under constant scrutiny Further research is necessary to determine the importance of the particle size of the dust in the pathogenesis of pneumoconiosis

What is the actual toxicity of silica? The diatomacious earth pneumoconiosis study indicated that noncrystalline forms of silica as well as cristobalite and tridymite produce a pneumoconiosis that is not silicosis per se but closely related to it The predominate opinion of investigators of coal miners pneumoconiosis is that the small concentrations of crystalline silica to which the worker is exposed have no significance in the etiology of the disease Others however maintain that these small concentrations may be significantly related to the problem

Management and Treatment of Patients with Coal Workers Pneumoconiosis is discussed by J C Gilson and G S Kilpatrick[6] Coal workers pneumoconiosis has two distinct related forms The first simple pneumoconiosis caused by gradual accumulation of the fine dust in the lungs is recognized radiologically by characteristic minute opacities The condition advances as such only if the miner continues to work in a dusty environment but it makes him liable to the second complicated form characterized by x ray appearance of additional larger localized opacities corresponding to the massive fibrosis found pathologically It progresses whether or not dust exposure is continued often develops after cessation of exposure to dust and is much the more disabling form It is believed to be caused by tuberculosis modified by presence of coal dust The only pathognomonic physical feature is expectoration of inky black sputum and this is likely to occur only in complicated pneumoconiosis Certain diagnosis can be made only on the basis of industrial history and chest x ray

Many patients find symptoms worst in the mornings in

(6) B r M J 1 994 999 Ap 23 1955

All patients had dyspnea fatigue and cyanosis of varying degrees before death with right ventricular hypertrophy on electrocardiograms Pulmonary hypertension was diagnosed in each patient but the antemortem diagnosis of periarteritis nodosa could not be established

The relation of periarteritis nodosa to systemic hypertension is controversial Pulmonary periarteritis nodosa is infrequent and the simultaneous occurrence of pulmonary hypertension and periarteritis nodosa limited to the lungs is especially noteworthy

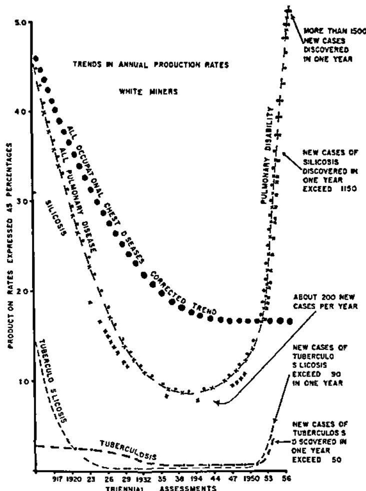
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PNEUMOCONIOSIS

Accomplishments in Epidemiologic Study of Silicosis in United States is discussed by *H N Doyle Victoria M Trasko W M Gafafer and S E Miller*[5] (Washington D C) Information on deaths from occupational respiratory diseases *in the United States* was provided by *the National Office of* Vital Statistics Over the four year period 1949 52 they reflect an average of more than 1 200 deaths/year from silicosis and anthracosilicosis combined over *600 deaths/year from* respiratory tuberculosis with mention of occupational disease of the lung and about 225 deaths/year from other pneumoconioses probably chiefly silicosis *Age or* occupational analysis of the deaths is not available Thus it is apparent that silicosis is still a major occupational disease in the United States Limited information however indicates that tuberculous infection is not so prevalent as it once was among silicotics and because of our present compensation laws and enlightened employment practices the disease no longer has extreme social consequences The data also indicate that there is a longer period of development of the disease than in the early days Average age of those with third stage silicosis in the tri state study of Oklahoma Kansas and Missouri in 1914 was 38 years It appears to be higher today

The age range of many of the silicotic patients indicates that they may have received their initial exposure before

(5) A M A Arch Indust Health 12 48 55 July 1955



F g 32—O p tion l h t d se W tw t ra d g ld m South Af ca (Cou y f S h pe G W H A M A A h I d t Health 12 33 47 July 19)

cold weather and during bouts of chest infection especially in winter. Alleviation of distress at these times depends primarily on controlling bronchospasm and chest infection. The former is frequently precipitated by sudden changes of temperature. Epinephrine is less dramatic in its effect in most patients than in typical asthmatics but is of real use given by injection or inhalation in acute attacks. In acute pulmonary infections penicillin in large doses combined with streptomycin 1 2 Gm daily is usually effective, the sputum changing rapidly in character and dyspnea and bronchospasm becoming less severe even if no antispasmodic treatment is given at the same time. An early morning cup of tea to which has been added the simple sodium chloride compound mixture (NF) may help bring relief in this period of acute distress from cough. Codeine is useful in treating unproductive and irritating cough. Men with complicated pneumoconiosis and a positive sputum usually react poorly to chemotherapy and rarely survive more than two years.

In the terminal stages of complicated pneumoconiosis cor pulmonale is common and is often precipitated by an attack of chest infection. After a period in bed and when cardiac failure has been controlled the patient is encouraged to be up and around as much as possible.

• [The pneumoconiosis of coal workers continues to receive relatively little attention in the American literature as a condition separate and distinct from the silicosis found in men who have worked in dusts containing a high proportion of silica. (See however Martin Am J Pub Health 44 58 1954 abstracted in 1955 56 YEAR BOOK pp 153 158.) In Great Britain this has in recent years become recognized as an important industrial disease and it has been the subject of extensive investigations by the Pneumoconiosis Research Unit of the Medical Research Council. Coal workers pneumoconiosis occurs not alone in miners but in other coal handlers such as trimmers who work at loading coal into the holds of ships. James (Brit J Tuberc 48 89 1954 abstracted in 1955 56 YEAR BOOK p 158) found the massive form of the disease to occur in significant numbers among such workers. This he believes disposes of the theory that the condition is due to highly siliceous dust from rock strata adjacent to the coal seams.—Ed.]

Occupational Chest Diseases in Gold Miners: Review of Progress in Union of South Africa is presented by G. W. H. Schepers[7] (Saranac Lake N Y). The spectacular initial decline around 1917 in the annual rate of production of silicosis tuberculosis and silicosis combined with tuberculosis among white miners is well shown in Figure 32 which in

(7) A M A Arch Indust Health 12 33-47 July 1955

the first 10 years and at a much more rapid rate than the 1918 cohort No explanation for this phenomenon is known

Pneumoconiosis on Kolar Gold Field South India Geoffrey E Ffrench[8] (Oakville Ont) defines pneumoconiosis in three stages (1) anteprimary—x ray evidence only without



Fg 33 —Th t sec on f l g f bl t g d 35 w th 17 yea d g ou d serv D t but on f d t in primary tag h se l a ly (C t y f Ffrench G E A M A A h I d t. Health 1 738 J l 1955)

(8) A M A A h I d t Health 1 73 82 J ly 1955

cludes only those cases discovered for the first time in miners who did not have silicosis *previously* Following an all time low of about 200 cases toward 1950 by 1954 the annual rate of certification exceeded by three times the highest rate recorded when pulmonary disease was most prevalent In the year 1953 54 more than 770 second stage silicotics and more than 400 third stage silicotics were discovered out of better than 30 000 men Against 150 new cases of silicosis in 1917 more than 1 050 first stage silicotics were found during the year 1953 54 to which must be added more than 490 men certified as having pulmonary disability in the first stage (equivalent to second stage silicosis) and more than 200 patients with pulmonary disability in the second stage (third stage silicosis) These cases certified for the first time in such *large numbers* represent persons whose disease *had not been* recognized until some time after the earliest detectable sign *or the relevant degree of disability had first become manifest*

The trends shown by the curves therefore more truly represent annual certification rates than annual production rates In the future when it has become known whether these trends are maintained or abruptly deflected and after belated certifications have been appropriately antedated it should be possible to decide whether the curve of progress should be redrawn at a generally decelerated rate as suggested in Figure 32 Clinical and autopsy experience tends to favor the latter prospect for the pulmonary disease as diagnosed in 1953 54 is not as florid as it was earlier in the century *perhaps because tuberculosis is less common in the* incipient stages The recrudescence of tuberculosis and tuberculosilicosis *does not mean a sudden spread of the* infection but prompter diagnosis In other words though in 1953 54 these cases were recorded as occurring in greater numbers than during the previous 30 years the disease had not necessarily become more prevalent perhaps all it means is that tuberculosis will no longer be reported for the first time after death

The death rate for tuberculosis has not abated significantly and may even be worse than during the past 40 years Thus whereas only *26% of the 1918 cohort of tuberculotic miners* survived after 20 years less than 22% of the 1938 cohort were alive *at the end of* 16 years the majority having died within

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(8) A M A A h I d t H lth 12 73 8 J ly 1955

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valid ty of conclusions derived solely from statistical studies of the kind which have been made in this fi ld (see Berkson s critique below) or who reject entirely the evidence incriminating smoking (Hueper p 149) and stress the importance of other and variegated environmental factors Stocks and Campbell (p 150) believe that both atmospheric pollution and smoking may be responsible and they suggest that 3 4 benzpyrene may be the single most important inhaled carcinogen since it is common to both cigaret smoke and the polluted atmosphere of urban and industrial centers This is advanced merely as a working hypothesis on evidence which as yet is little more than suggestive Should this hypothesis be substantiated it would mark a most important advance and would reconcile much of the evidence which now appears to be conflicting —Ed

Statistical Study of Association between Smoking and Lung Cancer is examined critically by Joseph Berkson[9] who believes that if an essential biologic association is to be con

TABLE 1—Data of American Cancer Society Study on Cigaret Smoking

A Y	C Sm %	Sm Tim % S m L
50-54	51 7	66 6
55 59	45 0	60 5
60 64	57 0	51 6
65-69	28 0	40 7
Totals		
50 59	48 5	
50-69	47 8	57 4

H mmond E C d Hor D R lat hip between b m m k g h b t d d th rat J A M A 155 1316 13 8 A g 7 1954

sidered proved the population must be an experimental one An association found in a purely statistical investigation made on an existent population i e an investigation which is retrospective as regards either variable should be accepted tentatively until fully corroborated experimentally Attention is called to the possibly fallacious character of a conclusion based on hospital populations dead or living It has been suggested that this concept might also apply to prospective studies

In their prospective studies Doll and Hill evaluated the association between smoking habits and mortality of physicians and Hammond and Horn the relation between these habits and death rates in a population which is an unknown fraction of the potential of solicited friends of member workers of the American Cancer Society (Table 1) It may be

(9) P oc Staff M t M y Cl 30 319 348 J ly 27 1955

disability (2) primary—x ray evidence with symptoms causing incomplete disability and (3) secondary—x ray evidence of pneumoconiosis with clinical and x ray signs of active tuberculosis and/or complete disability There are usually no complaints or clinical findings in the anteprimary stage which occurs in 64 93% of those classified as having pneumoconiosis Assessment of disability in miners of the Kolar gold field is often difficult because of unreliability of their symptoms and difficulty in carrying out even the simple tests required the significance of modern tests for pulmonary function would probably be equivocal

The dust is deposited in perivascular and peribronchial areas and in noninfective cases is not associated with significant fibrosis by ordinary staining methods One should not confuse the mass of dust cell aggregates with the typical silicotic nodule Large tissue sections show the distribution of dust in uncomplicated cases as well as the focal emphysema described (Fig 33)

If the quantity and percentage of hornblende schist in the air borne dust is reduced by change in rock formation or mining methods a higher quartz content might result leaving a greater proportion of silica that is not neutralized by aluminum oxide so that true silicosis might ensue

Pneumoconiosis on the Kolar gold field is primarily a radiologic condition but at any time might assume more serious proportions The relative harmlessness of the condition may be due to the relatively high aluminum oxide content of the air borne dust It is only when pneumoconiosis is associated with tuberculosis that life expectancy is shortened

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NEOPLASMS

In the past several years there has been great emphasis on tobacco smoking as the principal causative factor in the increased prevalence of lung cancer Some of the more important statistical studies pointing toward this conclusion were included in the YEAR BOOK for 1954 55 (pp 132 137) and for 1955 56 (p 151) In the past year there have been some further studies supporting the thesis that excessive smoking is a principal if not indeed *the* principal cause of epidermoid carcinoma of the lung Mostly these add little to the indictment except the weight of additional statistical material This has become sufficiently impressive so that many regard the causal relation between smoking and lung cancer as conclusively established There are however dissenters who either question the

TABLE 3 —DEATH RATES FROM SPECIFIC DISEASES IN CIGARET SMOKERS AND NONSMOKERS (AMERICAN CANCER SOCIETY)*

	D h ra 100 000 y									
	A l dis ses		C f		Oth		C ry d es		O d ce	
	C re		Cig		Cig m k		C k		C k rs	
	N	Yes	N	Y		Y	N	es	N	Y
0 54	602	955	5	46	91	103	30	442	74	365
55 59	1 72	1 3	1	89	158	1 2	440	7 7	454	515
60 64	1 444	375	6	103	5	367	59	1 095	6	811
65 69	63	1 59	45	1 7	3 8	502	1 115	1 439	1 144	1 191

Tw ty tl p (m d) w d f r ll p the Am n C e Soc ty t dy R t f l g d f r th d w e l l t d t hg k n th p t f th t dy (H mm d E C d H D J A M A 155 1316 1328 A g 7 1954)

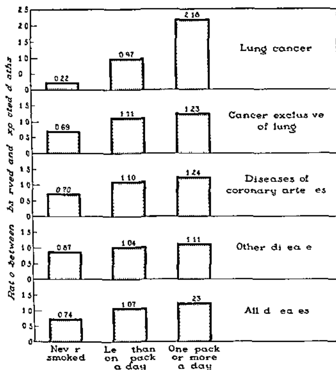
objected that both studies embraced only a selected population similar to investigations on hospital populations Nation wide statistical studies concerning smoking habits among males of different age groups have shown a higher incidence of smokers than the American Cancer Society study thus inferring that in the latter there was a tendency for cigaret smokers not to enter themselve with the result that the sampled population is selected

Comparison of death rates for United States males with those of the American Cancer Society study (Table 2) re

TABLE 2—COMPARISON OF DEATH RATES FOR THE UNITED STATES WITH THOSE IN AMERICAN CANCER SOCIETY STUDY*

[illegible]	De[illegible] [illegible] 100 000 [illegible]														
	Al[illegible]			[illegible]			Oh[illegible]			[illegible]			Oh[illegible]		
		ACS			ACS			ACS			AC[illegible]			ACS	
	US [illegible]	T[illegible]	N[illegible]	U[illegible]	[illegible]	N[illegible]	US [illegible]	T[illegible]	N[illegible]	US [illegible]	T[illegible]	N[illegible]	US wh[illegible] m[illegible]	T[illegible]	N[illegible]
50 54	1 06	838		3	3	6	318	11	91	4 6	171	3	58	315	4
55 59	1 8 1	1,349	1 1	8	1	17	9	1 8	1 8	1	614	44	816	491	451
60 64	93	1 9 5	1 131	114	5	6	406	8	9	1 18	8 1	5	1 3	19	6
65 69	4 189	2 9 3	66	1		43	7	416	358	1 478	1 4	111	1 15	1 1 3	1 144

* An[illegible] d[illegible]th [illegible] of the population of the American Cancer Society study were calculated by assuming a uniform exposure of [illegible] months (median) f[illegible] [illegible] that population Rate for United States white males [illegible] 195[illegible] [illegible] from Vital Statistics Special Report National S[illegible] (40 57 103 Dec 21 1954), of the U S Public Health Service National Office of Vital Statistics and a [illegible] refe[illegible] [illegible] (J M M yams)



F g 34 —I e f m t l ty w th m t f t g t m k g d t f Am C Soc ty t dy M t l ty m d n t m f t betw b d nd pe t d death (m th d f D ll R. d H ll A B B t M J 1 1451 1455 J n 26 1954) Amou t f mok g th g p g mou t m d l th / p k d y d 1 p k d y h ve b mb d b f 1 f gr on n g l d t g d g th tw m t d d th f m (Th g l ty f l pec fi g g oup d occ only w th d th gg t l l t n pos t (Cou t y f B k J P oc St ff M t M y Cl n 30 319 348 J l 27 1955)

1/2 1 pack a day or more than 1 pack a day is smoked (Hammond and Horn) then the finding can perhaps be regarded as evidence that spurious association can be produced in statistical data collected under other than strictly experimental conditions

Perhaps the general United States population is a better control group with which to compare death rates of the smokers than is the selected sampled population of nonsmok

veals that the latter are consistently lower One may conclude that in the response for volunteers to enter the survey men in relatively poor health tended to be excluded so that the population was selected favorably as respects death rate from all causes and from specific causes

The operation of selective forces in statistical investigations can be a subtle process and there are no factual studies to answer the question of their possible importance for the present situation nor is it conclusive that the published statistical studies all agree in showing an association between smoking and lung cancer On the contrary undeviating consistency of statistical results in support of the same conclusion is in some circumstances the hallmark of spurious statistical correlation If correlation is produced by some elements of the statistical procedure it will almost inevitably appear whenever the procedure is used

The American Cancer Society data on deaths from all causes and from various specific causes in smokers and nonsmokers of cigarets are shown in Table 3 In a sense these statistics support the hypothesis that cigaret smoking causes lung cancer since the age specific death rates from lung cancer for the cigaret smokers in the population are higher than those among the nonsmokers In another sense results do not corroborate this specific idea they prove too much The hypothesis that smoking causes lung cancer stands or falls with the conclusion that smoking causes also other cancer and coronary heart disease as well as other diseases The question is not Does cigaret smoking cause cancer of the lungs? so much as it is What disease does cigaret smoking not cause?

An increase of death rates with increase in the amount of smoking may be exhibited clearly by use of the index of Doll and Hill consisting of the ratio of the total observed to expected deaths for each class of amount of smoking (Fig 34) Doll and Hill considered the finding of association between death rate and amount of smoking the strongest evidence of a real association If one doubts that smoking can be so definitive a determinant of death that it affects differentially even deaths from causes other than cancer or coronary heart disease according to whether less than 1/2 pack a day

A prospective study on smoking and development of lung cancer should be based on an experiment in which persons randomly designated are subjected to various degrees of smoking with prospective observation on development of cancer This however is apparently impracticable But since in science there is no substitute for experiments an adequate program of experimentation with animals should be accomplished before definitive conclusions are drawn

It is unwarranted to conclude from previous statistical studies that a meaningful association already has been proved beyond doubt between cigaret smoking and lung cancer nor has causation between the two been established On the other hand at the very least these studies pose a strong presumption that smoking may cause cancer and/or may otherwise be deleterious to health and longevity

Environmental Causes of Lung Cancer are due to several atmospheric pollutants that may have additive cumulative and synergistic effects according to W C Hueper[1] (Nat l Inst of Health) Not all causative agents are known but those identified include dusts and fumes of nickel chromium compounds arsenicals asbestos coal tar soot vapors or mists of isopropyl oil petroleum derivatives and radioactive ores and gases Gasoline or Diesel engine exhaust atmospheric pollutants of English and American cities dust of asphalted roads and carbon black of automobile tires contain significant amounts of recognized cancer producing chemicals Industry related factors are important causally in the increase in lung cancers in industrialized countries during the last 50 years

Lung cancer death rates are significantly higher in urban industrialized areas than in rural areas especially among men whose occupations expose them to respiratory health hazards Discrepancies in the male female sex ratio of lung cancer are attributable to differences in exposure to known cancer producing atmospheric pollutants rather than to fluctuations in a single factor such as cigaret smoking Lung cancer death rates do not correlate with per capita consumption of cigarets in different countries but more closely parallel the rise in production and/or consumption of motor fuel coal tar petroleum products carcinogenic metals and miner

(1) P b H lth Rep 71 94 98 J ry 1956

ers of cigarets in the American Cancer Society study A comparison of the two surveys shows that only as respects deaths from coronary heart disease are the death rates of cigaret smokers consistently higher in the American Cancer Society study than in the United States males

An educational campaign on the inherent cancer hazards of smoking has been suggested Such a proposal seems poorly founded when data on which the conclusions rest disclose that the cigaret smokers in the American Cancer Society study have equal or lower death rates from cancer than the general public

Unfortunately the basis for considering smoking a cause of lung cancer is exclusively statistical If according to Hammond and Horn the cancerogenic effect of cigaret smoking can manifest itself in 20 months why cannot lung cancer easily be produced experimentally?

The most important known cause of cancer and some other disease notably of the cardiovascular system is age It might be said that smoking accelerates the rate of living and advances age and age causes cancer The supposed effect of smoking if it exists may be to stimulate those trophic processes that constitute the biology of aging

Doll and Hill have more carefully and critically analyzed their findings than have Hammond and Horn However *even their study group had been severely selected in general* and in favor of low death rates in particular Furthermore the percentage of smokers was lower in their cancer group than in the controls It is characteristic of published studies that the percentage of smokers among controls varies widely The material differences between the study of *Hammond* and Horn and that of Doll and Hill as regards association between smoking and diseases other than lung cancer and coronary heart disease demonstrate that the appearance of association between smoking and disease in statistical studies can be influenced by circumstances in which the sample is taken Evidence on whether or not the association shown in the prospective studies of Doll and Hill and of Hammond and Horn has been produced spuriously by selection will perhaps be provided in the projected study on the records of the Veterans Administration

of the population can account for only a small fraction of contrast in total rates and it was estimated that in the Liverpool area about half the deaths of men from lung cancer arose from cigaret smoking and about three fourths of the remaining half from a factor present in only slight degree in the rural area

Concentration of smoke and of 3 4 benzpyrene other polycyclic hydrocarbons and sulfur dioxide in the air rose with increasing urbanization the benzpyrene figure in Liverpool being 8-11 times as great as in the rural localities This ratio corresponded with estimated mortality ratio among non smokers living in these areas When death rates were compared with calculated total intake by different categories of smokers in the areas of benzpyrene derived from air according to certain assumptions plus that derived from the number of cigarets smoked degree of correspondence was such as to suggest that benzpyrene might be the one agent involved

The authors suggest that benzpyrene plays a dual part through cigarets and air pollution Such a working hypothesis may assist research in the field whether or not it is finally substantiated

Exfoliative Cytology and Pulmonary Cancer Histopathologic and Cytologic Correlation Harlan J Spjut Dorothy J Fier and Lauren V Ackerman[3] (Washington Univ) reviewed 501 cases of pulmonary cancer and their cytology obtained from 905 sputum examinations and 364 bronchial washings The cytology was positive in 31 6% of the bronchial washings and 27 1% of the sputa In 57 8% of all the cases the report was positive with an optimum number of specimen three or more 76 6% were positive Of 318 bronchial biopsies 66 3% were positive and only 28% of the positive biopsies were in operable cases

The highest percentage of positive smears from bronchial washings came from the lower lobe lesions while lesions in the left upper lobe yielded the highest percentage of positive sputa Cytology aided in diagnosing peripheral pulmonary cancers with the highest percentage of positive smears from lesions 2 3 cm in diameter and larger than 7 cm

(3) J Th S g 30 90 107 J ly 1955

als or the construction of asphalted roads No special lung cancer is characteristic for any special carcinogenic factor

Evidence for cigaret smoking as a major cause of lung cancer is inadequate Statistical association is absent between lung cancer and cigaret cough although such cough is characteristic of chronic chain smokers or between cigaret smoking and cancer of the lips and oral mucosa despite constant contact with tarry liquor oozing from the cigaret tips Though chronic smokers have notoriously dark brown stained fingers not a single case of cancer of the fingers is attributable to cigaret tar Experimental evidence at best only indicates the presence of mild carcinogenic agents in cigaret tar in hyperreactive animals there is no evidence that these experiments have any equivalent in man Such serious fundamental defects and contradictions diminish the importance of cigaret smoking in the etiology of lung cancer

Lung Cancer Death Rates among Nonsmokers and Pipe and Cigaret Smokers Evaluation in Relation to Air Pollution by Benzpyrene and Other Substances By means of data from the first two years of study of environmental histories of persons with and without cancer being conducted by the Cheshire and North Wales Branch of the British Empire Cancer Campaign Percy Stocks and John M Campbell (St Bartholomew s Hosp London) calculated death rates from cancer of the lung and bronchus among men of different smoking habits living in a rural area of Wales in a mixed area around Chester and Wrexham and in Liverpool county borough Death rates were then related to measurements of benzpyrene and other substances present in the air within those areas

Rural death rate increased proportionately to number of cigarets smoked per week and pipe smokers as a group ranked with cigaret smokers of about 25 a week Liverpool rates exceeded rural rates in every smoking category but urban rural ratio fell progressively from about 9 1 among nonsmokers to a small value approaching unity among heavy cigaret smokers Absolute urban excess was much the same in each smoking group suggesting that an urban factor is added to effects of smoking Differences in smoking habits

(2) B t M J 2 9 1929 O t 15 1955

this site has been assumed to be the origin but only in cases of small or early growths can the site of origin definitely be recognized

In the 123 resections in which the origin was definitely located 47 1% of the tumors were central 3 3% intermediate and 49 6% peripheral The most distinctive feature of the central tumors was bronchial obstruction present in all cases which was a useful guide in locating the tumor origin Peripheral tumors often showed central scarring and bronchial involvement when present was due to invasion from the primary growth directly or from secondary lymph nodes

Most mall tumors were central this type apparently producing symptoms early Giant and large tumors were mainly peripheral an indication that symptoms appear later in development of the disease peripherally

Of tumors whose origin was located the adenocarcinomas were always peripheral and the polygonal cell growths frequently peripheral Squamous cell tumors were most often central and oat cell carcinomas equally divided centrally and peripherally

The central tumors are probably favored for resection because they cause obstructive changes and chest symptoms even when small and many are diagnosed on bronchoscopic biopsy The peripheral tumors are unlikely to cause chest symptoms until they have spread to involve either the chest wall or the hilus By this time many are inoperable and if resectable very large The fact that more than 50% of tumors are of peripheral origin is largely responsible for the poor prognosis and low operability rate associated with lung cancer

Cytologic Studies of Sputum Secretions and Serous Fluids in Malignant Lymphoma were made by Clyde J Dawe Lewis B Woolner Edith M Parkhill and John R McDonald (Mayo Clinic and Found) in 82 patients with histologically proved malignant lymphoma Malignant disease was diagnosed in nine instances The lymphomatous nature of the process was recognized in four of these patients and was suggested in a fifth Three of the five subsequently showed manifestations of leukemia Three patients had

(5) Am J Cl P th 25 480 488 M y 1955

When hilar and bronchopulmonary nodes were involved the bronchial washings were more likely to be positive Positive smears were obtained in 56 1% of the operable and 59% of the inoperable cases In 59 operable cases cytology was the only positive tissue examination before surgery

Typing of positive smears was 79 3% accurate epidermoid carcinoma in 89 2% undifferentiated carcinoma in 76 2% and adenocarcinoma in 39 3% Two bronchiolar carcinomas were accurately typed from smears There were no false positive reports in three years Even one or two false positives are too many when a needless pneumonectomy is the result

Bronchial washings gave positive results more often than did sputa However sputum is readily and repeatedly available and inexpensive to procure In obtaining specimens from the site of the lesion bronchial washings are more selective and they are particularly important in patients with nonproductive cough

Cytology is of little value in localizing a cancer in the respiratory system Lesions in the right lung gave a higher percentage of positive smears than did the left Lesions in the periphery arising in bronchioles gave a low percentage of positive sputa or bronchial washings

With a positive biopsy the chances for operability are decreased A positive or negative cytology does not seem to alter the chance of operability Cytology in pulmonary cancer is of little or no prognostic value

Site of Origin of Lung Cancer and Its Relation to Histologic Type J B Walter and D M Pryce[4] (London) in a study of 207 resected tumors located the site of origin definitely in 59 4% and probably in an additional 18 4% in only 22 2% was the site in doubt Three general classifications were used central arising in one of the nominate bronchi intermediate from a large branch of a nominate bronchi and peripheral arising from a minute bronchus or bronchiole

The accepted teaching has been that most lung cancers arise in the major bronchi near the hilus This is based mainly on postmortem studies of the disease in terminal stages when the tumor is large and has spread widely Gross involvement of the large hilar bronchi is usually present and

(4) Thorax 0 117 126 J e 1955

current rise in the frequency with which the diagnosis of bronchogenic carcinoma is being made among tuberculous men over age 40

In these active cases of pulmonary tuberculosis of this series the advent of bronchogenic carcinoma did not block the discovery of tubercle bacilli in the sputa nor did progression of the carcinoma cause a reactivation of pulmonary tuberculosis when the latter was previously inactive

Certain x ray differences may favor bronchogenic carcinoma Infiltrates in the anterior segments of the upper lobe are often carcinomas since similar tuberculous lesions are more often located in the posterior segments Linear densities somewhat nodular and thicker than vascular shadows are at times roentgenologic expressions of carcinoma X ray regression of tuberculous densities on rest and adequate chemotherapy and simultaneous growth of another noncalcific lesion or failure to improve strongly indicates the coexistence of carcinoma of the lung and pulmonary tuberculosis

Patients with pulmonary tuberculosis present a unique opportunity for early discovery of bronchogenic carcinoma since they undergo frequent serial chest x rays With the increased frequency of lung cancers and with the shifting incidence of pulmonary tuberculosis into the older age groups the incidence of bronchogenic cancer in elderly tuberculous patients will also rise

LUNG ABSCESS

Acute Lung Abscess With Emphasis on Medical Aspects is discussed by S Aubrey Gittens and John P Mihaly[7] (Harlem Hosp New York) Lung abscess is definitely decreasing in incidence perhaps because of more liberal administration of the various antibiotics early in the course of any infectious disease The right lung is more frequently involved than the left The following are modes of pathogenic evolution in order of frequency aspirational inhalational neoplastic postpneumonic traumatic direct extension from adjacent

(7) Am J Surg 89 986 994 May 1955

Hodgkin's disease and positive cytologic findings in none was it possible to specify the nature of the disease except that it was malignant Rate of positive cell findings for serous fluids was 1 in 7 whereas that for bronchial secretions was 1 in 10 and that for sputum 1 in 13

Such figures do not indicate much value in the method if one assumes that examination is performed solely for proving diagnosis of lymphoma but in such cases other forms of disease particularly primary carcinoma of the lung must be considered With this view positive findings in lymphoma amount to a rather valuable by product of a method that can stand on its own merits in diagnosis of pulmonary carcinoma This applies to only four patients in the series—those in whom it was possible to identify cytologically the specific lymphomatous nature of the process

A less important clinical problem in which cytologic findings might help deals with patients with histologically proved lymphoma in whom signs of pleural or abdominal effusion subsequently develop Though it is obviously likely that such effusion is due to pleural or peritoneal involvement by lymphoma it would be advantageous to have positive microscopic evidence Positive results for malignant cells in only 5 of 36 serous fluids in the series would however appear discouraging

Diagnosis of Bronchogenic Carcinoma in Patients with Pulmonary Tuberculosis is discussed by Morton E Shafran and Julius Kavee[6] (New York) who found that in the literature of the past 20 years 114 cases of primary lung cancer have been reported among 7 847 autopsies on male and female patients with tuberculosis making an over all incidence of 1 45% of pulmonary carcinoma among tuberculous adults Incidence of bronchogenic carcinoma among tuberculous men over 40 is undoubtedly much higher than in the entire tuberculous population During a 12 month period at Montefiore Hospital the antemortem diagnosis of coexisting bronchogenic carcinoma and pulmonary tuberculosis was made and confirmed in six men over 40 constituting an incidence of 8 2% of coexisting pulmonary tuberculosis with bronchogenic carcinoma in this age group This suggests a

(6) A M A Arch Int Med 96 157 167 Aug 1955

putrid and 30% nonputrid infection Routine chest x rays did not show the characteristic fluid level in 30% of the patients Bronchoscopy done during the first 24 hours helps to exclude carcinomatous origin and to collect bronchial secretions uncontaminated by mouth organisms for study Besides routine smears and fungus cultures sensitivity studies are made for antibiotics because bacterial flora resistant to almost all available chemotherapeutic agents are met with disturbing frequency

Therapeutically bronchoscopy has long been advocated as essential to conservative management Infection in the lung like any other infection must drain adequately to clear If performed with thorough systematic aspiration of all branch bronchi broncho copy evacuates accumulated and obstructing bronchial secretions permits shrinking of the mucous membrane by topical application thus relieving further block and stimulates selective cough that makes continued effective raising of secretions possible Its beneficial effect lasts about 7 10 days

Postural drainage individualized according to the lobe affected and aided by an expectorant was continued as long as the abscess persisted

After bronchoscopy antibiotic therapy was started usually with penicillin Aqueous preparations were found superior to repository ones during initial therapy Penicillin was also given by the aerosol route 25 000 50 000 units every three hours during the day for three or four days A broncho relaxing drug such as neo synephrine® vaponefrin isuprel® or prothricin® providing a shrinking agent plus tyrothricin was added to each inhalation The antibiotic initially used may so change the bacterial flora as to become ineffective This is usually manifested by a reversal in response to therapy or by actual increase of the suppurative process on x ray

Unless there is definite x ray improvement at weekly intervals surgery should be considered if bronchoscopy and a change in antibiotic therapy are ineffectual Open drainage is indicated if a fulminating acute abscess is therapy resistant if the patient is a poor risk for resection or if there is a solitary peripheral uncomplicated abscess Resection performed under antibiotic coverage in 51 patients had a mor

organs and septic embolism less frequently they are due to bronchiectasis or bland pulmonary infarcts

Complications include spillage of infectious material through the bronchial tree causing daughter abscesses in ipsilateral or contralateral lung rupture of abscess into the interlobar fissure or pleural cavity causing localized or generalized empyema or into the bronchial tree and pleural space causing bronchopleural fistula and pyopneumothorax erosion of blood vessels causing hemorrhage and metastatic implantation of infectious material into other organs particularly the brain Ineffective healing may lead to lapse of an acute abscess into chronicity residual bronchiectasis remaining as a focus for future suppuration and extensive fibrosis

Successful medical management depends on prompt and adequate antibiotic therapy postural drainage and other supportive measures recognition and amelioration of coexisting medical and psychologic diseases marginal minor surgical procedures and early recognition of cases in which major surgery is indicated at the outset Of 73 patients with acute uncomplicated lung abscess 53 completed antibiotic treatment and were cured medically The number of patients requiring surgery will become increasingly smaller if prompt and adequate antibiotic and ancillary medical measures are instituted early in the course of acute suppurative disease of a primary nature

Lung Abscess—Medicosurgical Problem David H Waterman Sheldon E Domm and William K Rogers[8] (Knoxville Tenn) reviewed 464 cases observed since 1941 The series does not include mycotic infections bronchiectasis or tuberculosis 187 (40 3%) patients had carcinoma with secondary suppuration Adenoma led to suppuration in three patients and embolic abscesses in six High incidence of carcinoma and ever increasing occurrence of bronchogenic carcinoma strongly suggest that every case of lung abscess whether acute or chronic be carefully investigated for malignant background

The authors report the regimen which proved the most efficacious in the other 268 patients of whom about 70% had

(8) Am J Surg 89 995 1001 May 1955

groups predominantly in males Exposure to dusts containing organic material especially from domestic fowl or pigeon coops or dust of threshing filling silos or handling raw wool was significant in the etiology of the disease Farmers and their families and rural residents were most frequently affected

In the observed 229 patients pulmonary histoplasmosis was a mild self limiting infection with an excellent prognosis No deaths occurred Relapses occurred in seven patients but recovery followed with no interference with normal working capacity One patient required hospitalization three times during a 10 year period for exacerbations

The roentgenographic course of the disease is not characteristic and may be similar to tuberculosis or other chronic lung infections Disseminated pulmonary disease in which there is calcification especially in endemic regions can usually be attributed to histopla ma Symptoms of both disseminated and nondisseminated pulmonary histoplasmosis resemble acute respiratory infections and the diagnosis is usually not suspected unless a chest x ray reveals chronic lung disease

Nocardiosis Clinical Bacteriologic and Pathologic Aspects in seven cases are presented by Lyle A Weed Howard A Andersen C Allen Good and Archie H Baggen toss[1] (Mayo Clinic) Pulmonary disease usually presented as cough with thick sticky mucopurulent or purulent sputum Temperature varied from normal to 105 F The portal of entry in each patient was probably the respiratory tract but entry is possible through a break in mucosa or skin with subsequent dissemination Nocardia asteroides has been cultured from all parts of the body the most frequent extra pulmonary site being the central nervous system

Roentgenograms were not diagnostic of nocardiosis Abnormalities varied from a localized small area to bilateral patches of consolidation Two patients had localized pneumonia in two the disease was disseminated when first seen and in another it became disseminated during observation In one patient pleural fluid accumulated after therapeutic pneumothorax

(1) N w E gla d J M d 53 1137 1143 D 9 1955

tality rate of 1 9% Segmental resection was done whenever possible Empyema remains a grave problem particularly after pneumonectomy in which the incidence was almost 50%

MYCOSES

Chronic Pulmonary Disease in Histoplasmin Reactors Review of 229 Cases Discovered through Chest Clinic Examinations *According to* F Clark White[9] *(Ray Brook N Y)* histoplasmosis is a benign condition of common occurrence and wide distribution *readily confused with pulmonary* tuberculosis and rarely a fatal generalized disease

All the patients lived in upstate New York and were in two main groups from mountains and from plains All patients had demonstrable pulmonary infiltrates for at least two months 106 reacted to intradermal tuberculin tests 123 did not and all reacted to the intradermal histoplasmin tests

Patients who had histoplasmosis which was not disseminated had mild symptoms Of 18 patients 3 had no symptoms and 15 had cough lassitude chest pains expectoration fever weight loss hemoptysis dyspnea wheezing chills anorexia and generalized aching The symptoms tended to disappear after six weeks The same symptoms occurred in the patients with disseminated lung disease but were moderate to severe

Physical findings were limited *Râles* were found in six patients rhonchi in two and friction rub in one In both disseminated *and nondisseminated forms of the disease the in*filtrate appeared irregularly mottled in x rays The mottling shrank and became nodular then appeared as smaller spheres or ovals 1 20 months later Calcification usually appeared first in the center of the nodule 3 15 years after onset The central calcification did not increase in size but the less dense shadow surrounding it gradually cleared during the next 6-13 years Hilar adenopathy usually cleared within four months but occasionally persisted for five years Hilar calcifications have been demonstrated 3½ 10 years after onset

Pulmonar histoplasmosis was found among all age

(9) Am. t.. T berc 7 2 4 93 S pt mbe 1955

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(9) Am. Rev Tuberc 2 274 293 September 1955

(Fig 35) Even this finding is not definitive accurate diagnosis requiring bacteriologic identification

Nocardiosis should be suspected when acute or subacute pneumonia does not respond promptly to the usual antibiotics such as penicillin or tetracycline When the diagnosis is established sodium sulfadiazine 6-10 Gm daily should be started orally Ideal blood concentration is 16-20 mg /cc Duration of therapy depends on severity of disease and response to medication Surgical drainage or excision of abscesses may be necessary Adequate rest and nourishment are desirable

Results of 2 Hydroxystilbamidine Therapy in Disseminated Coccidioidomycosis are reported by I Snapper Lyle A Baker Bernard D Edidin and Daniel S Kushner in seven patients In five the disease was suppressed as manifested by progressive subsidence of complaints weight gain and resumption of normal activity In one progressive coccidioidal meningitis went into remission coincident with high dosage totaling 23 Gm In all five patients low grade infection persisted and serologic improvement during and after therapy was small The activity of the acute infection was probably markedly reduced Even with the large total dosage tissue concentrations were probably inadequate but gastrointestinal and general toxic symptoms precluded larger doses

No serious toxic effects were noted No patient had renal or hepatic toxicity Facial numbness mild neuropathy nitritoid reactions formication nausea and vomiting were noted Side effects were most marked in patients with severe chronic illness and constitutional complaints before therapy While 2 hydroxystilbamidine did not cure the disease it probably is valuable in therapy Longer follow up in a larger number of patients seems indicated

Treatment of Pulmonary Blastomycosis This disease is the rarest and most lethal of the three common pulmonary mycotic infections North Carolina is the center of the endemic area for North American type blastomycosis Two forms of the disease are recognized Cutaneous blastomycosis occurs in about half the cases and is probably due to dis

( ) A I t M d 43 71 86 A gu t 1955

Anemia leukocytosis and increased sedimentation rate are common but nonspecific Diagnosis depends on bacteriologic demonstration of the organism and recognition is important since effective chemotherapy (sulfadiazine) is available The micro organisms grow as fine branching filaments that may fragment into bacillary or coccoid forms Some strains are acid fast An occasional colony may contaminate sputum cultures but should not be considered causative unless the colo



Fig 35 —Ab f uppe l l f ght lung d t oc d Not l l g my l a B w G am t ×1 400 (C t y f W d L \ t f New E gl d J M d 253 1137 1147 D 9 195)

nies are numerous on repeated culture and no other recognizable pathogen can be found Bronchoscopic material or lung biopsy may be necessary to establish the diagnosis

The lesions were necrotic and suppurative and contained a few macrophages They did not resemble granulomas had no epithelioid cells and only occasional giant cells Fibrosis was minimal Organisms were not visible with hematoxylin and eosin stain and were seen only with special stains such as the Brown Gram technic They formed gram positive (granular) branching mycelia approximately 1 μ in diameter

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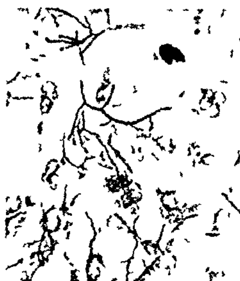


Fig 35—Absce f u(pe)) f ght l ng du to noca di N e l h ng my el a B ow G m st n ×1 40) (Cou t y f W d L A t of New E la d J M u 253 1137 1141 Dec 9 195)

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( ) A J Med 43 71 56 August 1955

semination of a recognized or unrecognized primary pulmonary focus The respiratory tract is thought to be the portal of entry for the systemic type in which the lungs bones and lower genitourinary tract are most commonly involved In many patients both skin and visceral manifestations are present

Timothy Takaro James E T Hopkins and James D Murphy[3] (V A Hosp Oteen N C) report on 14 patients with pulmonary blastomycosis All were young men In most patients onset was characterized by productive cough Chest pain occurred in six and hemoptysis in five Diagnosis was based on study of the sputum in nine on biopsy of skin bone or of the surgically resected specimen of lung in four and on *study of the prostatic smear in one*

Iodides were used alone or with other forms of therapy in eight patients four died two recovered after iodides were discontinued and other agents used and two remained clinically well but were carrying the organisms in the sputum Potassium iodide therapy was not satisfactory

Undecylenic acid was given to seven patients two of whom had been treated originally with iodides Initial dose of 5 Gm /day was rapidly increased to maintenance dose of 10 25 Gm /day Average duration of treatment was 40 weeks and average total dose 4 596 Gm Evidence of the value of undecylenic acid was clearcut in three patients and strongly presumptive in two In three clinical improvement *occurred but curative results were not obtained* Stilbamidine was given to four patients intravenously in doses of 150 mg /day Marked clinical improvement was noted in two and some degree of improvement in all four

A completely satisfactory form of treatment for pulmonary blastomycosis has not been found Pulmonary resection for localized stable lesions after immunologic balance is obtained may be an important therapeutic aid *Combined therapy* with undecylenic acid and one of the diamidines may be the best method of drug therapy available

Pulmonary Moniliasis Treated by Brilliant Green Aerosol Report of Case is made by Cadiel M Smith and Robert N Armen[4] (V A Hosp Wilkes Barre Pa) Monilia natu

(3) D Che t 28 03 16 A gu t 1955
(4) Ann I t Med 43 130 1309 December 1955

ral saprophytes and normal inhabitants of the mouth throat and respiratory tract are potentially but only occasionally pathogenic Unequivocal diagnosis is difficult because the infection is found in normal persons commonly coexists with other pulmonary infections and strains virulent to experimental animals may be harmless in man The most reliable criterion is persistent isolation of the fungus from bronchial washings and sputa in absence of all other possible causal agent but with presence of clinical and radiologic pulmonary disease Immunologic responses and response to the intradermal test are not always positive

Clinical manifestations are not specific or characteristic but are common to other bronchopulmonary infections Cough expectoration hemoptysis dyspnea pain weight loss weakness lethargy fever and sweats may all be noted The infection may be acute and fulminating lasting a few weeks or slow and chronic lasting years and simulating pulmonary tuberculosis bronchiectasis or carcinoma Radiologic lesions are not specific and may appear as diffuse widespread infiltrations in one or more lobes indistinguishable from tuberculosis or granuloma The extensive peribronchial thickenings are usually hilar but may be scattered or patchy are larger than those seen in miliary tuberculosis may fluctuate from week to week and may result in cavitation Healing is usually by extensive fibrosis

In the authors patient Candida albicans was cultured from sputa bronchial washings pleural fluid and lung biopsies Tuberculosis was excluded by repeated negative cultures of sputa and bronchial washings Therapy was begun with 2 cc of 0 1% brilliant green in 50% propylene glycol by oxygen aerosol inhalations five times daily increased to 0 2% a week later He received many interrupted 2-4 week courses of treatment over about 7½ months Clinical response to the therapy was clearcut He is the second reported patient apparently cured by brilliant green

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PLEURISY PNEUMOTHORAX

Primary Serofibrinous Pleural Effusion in Military Personnel William H Roper and James J Waring[5] (Univ of

(5) Am R T b 72 616 634 S pt mb 1955

Colorado) report 141 cases of primary serofibrinous pleural effusion in young men who were followed for five years or more All had positive reactions to tuberculin intracutaneously None was treated for the initial illness Men who were less than age 25 when they first had an effusion were more likely to develop active tuberculosis (75 3%) than those age 25 or older (54 4%)

The original effusion contained tubercle bacilli in 51 patients Relapses later occurred in 33 of these Of 90 patients whose original effusions were either inadequately examined or were negative for tubercle bacilli 59 later developed tuberculosis Presumably many if not all effusions in these patients were originally tuberculous Of those without adequate bacteriologic study 71 4% had recurrence of effusion with active tuberculosis and 60 4% of patients with sterile fluids later had evidence of tuberculosis

Relapse was as frequent with small as with larger effusions In none of the patients did a pulmonary parenchymal lesion later develop in an area originally obscured by fluid

Of 66 patients allowed to return to normal physical activity after brief hospitalization 91% relapsed Of the 92 patients who developed active tuberculosis 90% did so within three years of the original pleural effusion

In young adults acute serofibrinous pleurisy with effusion is practically always due to tuberculosis The pleurisy often is a local and dominant manifestation of a disseminated infection or disease The underlying disease is prone to relapse like all tuberculosis and the patient must be treated accordingly

• [This careful study emphasizes again the strong probability of tuberculosis as the cause in most cases of idiopathic pleurisy with effusion and the dangers of neglecting appropriate therapy of this early manifestation of tuberculous disease Most experienced clinicians will agree that in the absence of evidence to the contrary these *primary* effusions in young persons should be regarded as tuberculous and treated accordingly Diagnosis based only on probability is however unsatisfactory and insecure Better and more prompt methods of specific diagnosis are nowhere more needed than in this common condition of pleurisy with effusion Perhaps pleural biopsy (see next article by Small and Landman) will provide the solution to the dilemma As the prevalence of tuberculosis declines probability as a diagnostic criterion will become less satisfactory even than it is now and relatively less reliable —Ed]

Etiologic Diagnosis of Pleural Effusion by Pleural Biopsy

In five patients with pleural effusion seen by Maurice J

Small and Milton Landman[6] (East Orange N J) no diagnosis could be established bacteriologically and in each the diagnosis of tuberculosis was made by biopsy of the pleura Because of the surprisingly large amount of tuberculous tissue present these findings cast doubt on previously accepted concepts of the pathogenesis of pleural effusion of tuberculous etiology

Pleural effusion in previously healthy young adults is a diagnostic problem Various laboratories report 50 90% success in demonstrating tubercle bacilli in pleural fluid but in many patients no diagnosis can be confirmed Pleural biopsy neither difficult nor dangerous when done by thoracic surgeons provides a definite diagnosis rapidly and is recommended for routine use in pleural effusions of undetermined etiology

TECHNIC —*With the patient supine an appropriate intercostal incision* about 8 cm long is made through all layers to the parietal pleura An oblong section of parietal pleura approximately 1 5 X 3 cm is excised The pleural space is observed and the underlying lung *palpated After aspiration of all available fluid the wound is closed* in layers with an indwelling 22 F catheter which is removed at the end of the procedure after aspiration of air and fluid

Needle Biopsy of Parietal Pleura Preliminary Report In tuberculous patients with serofibrinous pleurisy it is often difficult to isolate the Mycobacterium tuberculosis from the sputum gastric washings and pleural fluid Often specific therapy must be instituted before definitive bacteriologic diagnosis can be established

Nicholas DeFrancis Emanuel Klosk and Edwin Albano[7] (*Harrison S Martland Med Center Newark N J*) developed a technic that may obviate prolonged diagnostic procedures

TECHNIC—The patient is premedicated with *demerol*® and a barbiturate The biopsy site is prepared with tincture of merthiolate® and alcohol Procaine 2% is used for local anesthesia which is carried down to the pleura With the patient in the sitting position a small skin incision is made at the biopsy site and a 17 gauge needle to which a 50 cc syringe is attached is inserted into the appropriate interspace along the upper margin of the lower rib Constant traction is applied *on the plunger of the syringe while the needle is advanced* At the first sign of withdrawal of pleural fluid the needle is withdrawn a fraction of an inch and a Kelly clamp is applied to the

(6) J A M A 158 907 912 July 16 1955
(7) New England J Med 252 948 949 J n 1955

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ic cavity is carefully inspected before closure A membrane may form on the denuded chest wall if the lung does not immediately expand Drainage for 24 hours insured adequate contact in all nine patients None showed Horner s syndrome (previously reported in 39% of all patients requiring extensive apical extrapleural dissection in the presence of empyema and thickened pleura) or loss of pulmonary function Artificial pneumothorax could not be induced and there have been no spontaneous recurrences on the side operated on

Pleurectomy is preferred over chemically or mechanically induced pleuritis because complications are fewer hospitalization is shorter the potential pleural space is obliterated and chances of recurrence are eliminated

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TUBERCULOSIS

Key to Interpretation of Pathogenesis of Tuberculous Lesions Increased Importance of Giant and Epithelioid Cells in Pulmonary Tuberculosis under Influence of Chemotherapy Georges Canetti[9] (Paris) describes and discusses an apparently paradoxical phenomenon in tuberculous lungs treated by chemotherapy i e the increased significance of specific cellular metaplasias (epithelioid and giant cell) These formations are of much greater extent in proportion to other noncicatricial tuberculous elements (inflammations necroses) than in nontreated tuberculous lungs Their morphologic appearance is diverse in regard to extent as well as location grouping of cells and cellular structure

Classic sites of cellular metaplasia are at the periphery of solid caseous strands at the center of incipient sclerotic zones and in bronchial walls They are also sometimes seen at the edge of cavities and in the alveoli Grouping of metaplastic cells is often of classic follicular type with giant and epithelioid cells at the center and lymphocytes at the periphery Variant groupings include lymphocytes surrounding a central giant cell with epithelioid cell thrust to the periphery or totally absent Cellular elements also may be totally dissociated with bands of pure epithelioid cells lacking giant

(9) P esse méd. 64 129 133 J 5 19 6

shaft of the needle adjacent to the skin The needle is then withdrawn completely and the same distance (from Kelly clamp to tip) is measured off on the Vim Silverman needle with the biopsy shaft inserted A Kelly clamp is applied to the biopsy needle marking off this distance The biopsy shaft is then withdrawn and the obturator inserted The needle is advanced through the skin incision to the distance marked off by the clamp The obturator is removed the biopsy shaft inserted the clamp removed and the outer needle carried forward about 1 9 cm while the biopsy shaft is held in place Both portions of the needle are rotated through 360 degrees and withdrawn together The biopsy shaft now encompasses the sample of tissue The skin is closed with one silk suture and a sterile dressing is applied

Pleura was obtained in each of six biopsies No hemorrhage pneumothorax pleural contamination or sinus tract formation occurred The method is most informative in patients with thickened pleura without pleural effusion and with or without demonstrable underlying pulmonary disease It may sometimes represent the only method of pathologic diagnosis in a primary pleural mass without actual thoracotomy The procedure is painless with minimal discomfort to the patient

• [This procedure is not recommended for patients with minimally thickened pleura It is therefore not as widely applicable as the surgical method of pleural biopsy suggested by Drs Small and Landman (p 164) —Ed.]

Parietal Pleurectomy for Recurrent Spontaneous Pneumothorax According to Edward A Gaensler[8] (Boston) exploratory thoracotomy and local wedge or segmental excision of the causative lesion is the preferred treatment Parietal pleurectomy was devised for cases in which subpleural involvement was too extensive for resection This procedure in which the parietal pleura overlying the affected area is removed by blunt dissection through a posterolateral incision may be applicable to patients with recurrent or chronic pneumothorax who have no detectable abnormality of the lung surface or who have multiple cracks or leaks of the visceral pleura without associated blebs It should be considered when patients have had two or more episodes of spontaneous pneumothorax *on the same side*

In eight patients no postoperative complications occurred but in one considerable amounts of blood drained from the side operated on Hemothorax should not occur if the thorac

(8) S g Gy ec & Ob t 10 293 308 M b 1956

giant cells is a dominant histologic feature of pulmonary tuberculosis under chemotherapy

The phenomenon of cellular metaplasia is a transient phase The lesions may progress to caseation and even to liquefaction of caseous material in chronic cases they tend toward absorption and sclerosis Of 174 cases of pulmonary tuberculosis treated by resection after chemotherapy such lesions were encountered in 106 (60%) In 60 (34%) giant and epithelioid cells were numerous and in 46 (26%) they were moderately increased Increase in cellular metaplasia is seen regardless of the chemical agent used but it may be influenced especially by isoniazid Cellular metaplasia is considerably more common in resected parenchyma containing a bacilliferous lesion (cavity or soft caseous lesion) Cultures were positive in 88% of cases with cellular metaplasia and in only 31% of cases not exhibiting these lesions

Experimental results show that specific cellular metaplasias are due to disintegration of tuberculous bacilli within macrophages Thus increase during chemotherapy is not paradoxical but is the direct consequence of bacteriostatic or bactericidal action of chemical agents and the lesions are the histologic sign of such intervention Neither the mechanism of evolution nor adjuvant causes which may contribute to metaplasia are fully known

Existence of cellular metaplastic lesions necessitates modification of current conceptions of the histology of tuberculous lesions Huebschmann s histogenic theory generally accepted for more than 30 years postulates the stages in evolution of the tuberculous focus as an initial stage of tissue damage then exudation caseation and follicular reaction In view of the developments described caseation of lesions of cellular metaplasia can no longer be considered exceptional Appearance of cellular metaplasia contrary to this theory never presupposes caseation at the center of the focus and it may progress from the exudative stage Even the initial exudative stage itself may be lacking the lesion from its onset consists of epithelial and giant cell transformation of macrophages In Huebschmann s idea of progression multiplication of bacilli is not arrested until there is caseation but another type of evolution may occur in

cells or conversely nests of giant cells in which almost every epithelioid cell seems to display atypical mitosis Pure lymphoid masses with abundant plasmocytes are common representing a *late* manifestation coexistent *with* extensive scleroses often with a bronchiole at the center

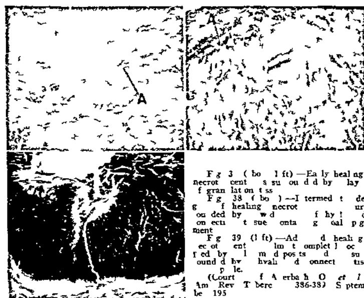
Epithelioid cells display marked polymorphism with all transitions between large rounded macrophages with regular opaque nuclei and the classic elongated epithelioid cells with irregular pale nuclei Giant cells show even

F g 36.—G nt c ll w th enormou n lu on of S h mann body type Pat t h d ece ed i on d a d p m l yl c a d (P \S) f two month d i p tom in d PAS for f month M on t h m ×380 (C rte y of Ca ett G P es e med 64 1 9 133 Ja 25 1956)

greater diversity cells of the Langhans type of moderate size with coronal or polar nuclei appear frequently and atypical forms are abundant Nuclei may be scattered throughout the cytoplasm grouped in irregular masses disposed *in* a double crown cells may assume bizarre shapes and the size may become huge with diverse inclusions such as crystals fat asteroid bodies or Schaumann bodies as in Figure 36 The giant cell may lose all definite borders resembling at times a diffuse syncytium as from *an agglomeration of new cells and* sometimes appears to be a single cell in the process of dissociation into numerous daughter cells Polymorphism of

pneumonia At first this zone is rich in fibroblasts epitheli oid and Langhans giant cells the capillaries are dilated and few collagen fibrils are present I iquefaction may occur and the cavity become evacuated with necrotic fragments re maining to line the inner wall The zone of granulat on tissue encircles the necrotic fragments

As healing continues collagen fibril laid down by fibro blasts and epithelioid cells increase in number and capillar



F g 3 (bo l ft) —Ea ly heal ng necrot cent s su ou d d by lay f gran lat on t ss

F g 38 (bo) —I termed t de- g f healing necrot ur ou ded by w d f hy l d on ectı t sue onta g oal p g ment

F g 39 (l ft) —Ad d heal g ec ot ent lm t omplet l oc r ed by l m d pos ts d su ound d by hyalı d onnect tıs- p le.

(Court f A erba h O et l Am Rev T berc 386-383 S ptem be 195

ies and cells decrease until the capsule consists of dense hyaline connective tissue The capsule contracts the necrotic center is compressed fluid is ab orbed and the area becomes dry and firm Cholesterol is first deposited in the necrotic zone when the capsule shows hyalinization and calcium ap pears in the necrotic area when hyalinization is complete or nearly so The first calcium deposits appear in the periphery of the necrotic zone as fine stippling

In this study tubercle bacilli were recovered in all of 29 howing early healing (Fig 37) from 6 of 14 showing an in

which bacterial growth is checked at the beginning even before appearance of a true exudate Chemotherapy in multiplying the cases of early arrest of bacillary growth brings into full view the course of the lesion Cellular predominance (even approaching a resemblance to tumor) was well known to earlier authors thus conceptions of histogenesis of tuberculosis are reverting to those current a half century ago

• [It is often stated that antimicrobial therapy affects the rapidity and degree of healing changes in tuberculous lesions (particularly the resolution of exudative components) but not the character of the pathologic tissue reactions These careful histologic studies of Dr Canetti indicate on the contrary that the morphology of the disease is often markedly altered under drug treatment—a phenomenon which has hitherto received little attention However Flory *et al* as early as 1948 (Am Rev Tuberc 58 421 1948) noted the increased numbers of giant cells Denst (Am Rev Tuberc 68 144 1953) described the pleomorphism of the giant cells and their appearance in unusual locations out of context with the other elements of a tubercle He is among the very few who have commented on the probable significance of these manifestations which he found in isoniazid treated patients Schaumann bodies were noted by Denst and also by Poppe de Figueiredo and de Paola (Am Rev Tuberc 71 186 1955) —Ed]

Effect of Degree of Healing on Persistence of Tubercle Bacilli in Pulmonary Lesions is discussed by Oscar Auerbach Gladys L Hobby Maurice J Small Tulita F Lenert and Laurence H Vaughan[1] (East Orange N J) In previous reports it was noted that tubercle bacilli remain viable in necrotic foci in patients who have received prolonged courses of chemotherapy No correlation was noted between the frequency with which viable cells [i e bacilli—Ed] were detected and the (1) duration of preoperative chemotherapy (2) total duration of chemotherapy (3) preoperative regimen, (4) length of time the patient was not infectious before surgery or (5) morphology of the lesion i e the degree of closure of the cavity Sixty five closed lesions were further studied to determine under what conditions tubercle bacilli survive

The development and healing of pulmonary tuberculosis are generally orderly and predictable The lesion in the adult most often appears in the upper lobe in the posterolateral aspect about 2 cm above the interlobar fissure The first change is bronchopneumonia rapidly becoming necrotic with an area of granulation tissue around the tuberculous

(1) Am Rev Tuberc 72 386 389 September 1955

surgically resected specimens from patients with pulmonary tuberculosis revealed cavitary lesions in 240 These could be classified into five types I thin walled (10 8%) II thick walled (66 3%) III open healing (9 6%) IV widespread fibrocaseous disease with ulceration (10 4%) and V shelling out of solid lesions (2 9%)

Open healing was seen in 25 specimens Grossly the



F g 40 — H g ca ty ppe port on of l ft l g Adm on film (F b 27 1953) h w d d f on P m periton m w t t d on A g l 1953 (Th film w m d w k bef g ry Th pat ent ecei d t ptomy d PAS f long th on yea d on d f tw month bef g y—M 15 1954) (Courtesy f Th mpson J R. Am R T be 72 158 170 A gu t 1955)

lining membrane of the cavity was smooth and glistening and in many instances transparent (Figs 40 and 41) Histologic study of these cavities revealed a monotonous picture of a dense fibrous tissue wall with some hyalinization and a few scattered lymphocytes Occasionally an area of calcification was noted and single or aggregate atypical giant cells were seen None of the cavities showed epithelization of the

termediate degree of healing (Fig 38) and from only 3 of 22 showing advanced healing (Fig 39)

As the signs of activity diminish and the caseou material becomes more solid tubercle bacilli are less frequently re covered from closed caseous lesions Similar findings have been reported for nodules Lessening activity is manifested morphologically by hyalinization of the capsule and deposi tion of calcium in the necrotic center

In other reported series the frequency with which tuber cle bacilli were recovered from closed lesions varied from 72% in recent or softened nodules to none in chalky or calci fied nodules In the authors series the frequency varied from 100% to 12% in these two groups respectively The fre quency with which tubercle bacilli can be recovered from closed necrotic lesions is directly related to the anatomic age of the lesion

• [The authors mention that these data are in agreement with the views of Canetti (*The Tubercle Bacillus in the Pulmonary Lesions of Man* [New York Springer Publishing Co 1955]) who similarly finds that the frequency with which tubercle bacilli may be recovered from closed lesions decreases as the signs of activity diminish and the caseous mate rial becomes more solid They also cite Hall and Gleason (*Transactions of 12th Conference on Chemotherapy of Tuberculosis* U S Veterans Administration 1953 p 219) who likewise observed a decrease in the frequency with which tubercle bacilli may be recovered from nodules in proportion to the histologic signs of activity

Dr Auerbach and his collaborators commented previously (Am Rev Tuberc 70 191 1954) that they found no correlation between the fre quency with which viable bacilli were detected in closed lesions and the duration of preoperative chemotherapy They agree however with Ca netti that this does not exclude the possibility that such therapy may play a part in changing the state of a lesion from that of caseation by collage nous replacement into that of fibrous tissue Dr Auerbach gives as his own opinion moreover that prolonged use of antimicrobial agents (strep tomycin isoniazid para aminosalicylic acid) does in fact shorten the pe riod of time required for healing of these foci and that calcification occurs in a shorter period of time —Ed]

Character of Tuberculous Cavities as Seen in Surgically Resected Specimens J Robert Thompson (Mun Tubercu losis Sanitarium Chicago) points out that considerable vari ation in the pathologic lesions in surgically resected lungs is to be expected because the disease process is interrupted at different stages of healing whereas autopsy specimens usu ally present the picture of terminal disease A review of 335

( ) Am Rev T berc 7 158 1 0 A gu t 1955

by artificial attempts at cavity closure such as pneumothorax thoracoplasty pneumoperitoneum etc by the type of drug therapy and by the nature of the pre existing lesion such as tuberculomas Open healing is probably related to present day chemotherapy especially with isoniazid

Bacteriologic study of 45 consecutive specimens showed positive evidence of tuberculosis in 40% (table)

• [Dr Thompson remarks that open healing was not found in any of the specimens from the resection of 1949 and 1950 and in only one case in 1951 In 1953 there were 13 such cases This suggests a correlation not only with the introduction of isoniazid in 1952 but with the lengthening of the duration of preoperative antimicrobial therapy which in mo t clinics has taken place gradually since 1949 50 One of the crucial questions of the next several years will be whether by further prolongation and intensif cation of antimicrobial therapy and perhaps the scovery of even better agents than we now have the occurrence of this type of healing may not be raised from less than 10% to a more su taut al figure —Ed]

Review of 138 Cases of Closure of Tuberculous Lung Cavities under Chemotherapy is presented by J D Ross and D T Kay[3] (Univ of Edinburgh) hemotherapy alone was

INCIDENCE OF RELAPSE RELATED TO DURATION OF CHEMOTHERAPY AFTER CAVITY CLO URE

	S g cal G p			Co ser G oup			C mb ned G p		
D f dru m h f ca y los re	<4	4–8	8+	<4	4–8	8+	<4	4–8	8+
N mbe f case	13	16	13	1	17	26	25	33	39
P rso mo h bserv d ce ca y l	91 5	311	12 5	2 6	327 5	267	517 5	638	39 5
R l pse		0	0	3	1	0	5	1	0
R l pse ra pe 100 perso years	8 2	0	0	15 9	3 7	0	(2 01) 11 6	(2 5) 1 9	(1 4) 0
	3 3			5 9			4 7		

P b tw E pec 0 0 l d 0 05 l p h wn n p th f mb d g oup X t t h w

given to 92 patients 46 had major or minor surgery also The relation between duration of chemotherapy and relapse was studied (table) No statistical difference was noted between relapse rate in conservatively treated and that in surgically treated patients after chemotherapy was discontinued

Cavitation in pulmonary tuberculosis has long been re

(3) Th 11 1 9 M h 1956



F g 41—S m Upp po t n f l ft l ng h w ng h g th n w ll d c ty w th m th l g d l t b l ng th ough t—t k g xample of op n h l g (Courte y f Thomp o J R Am R v T b rc 7 158 1 0 A g st 1955)

BACTERIOLOGIC DATA ON MATERIAL ASPIRATED FROM BRONCHIAL TREE OF 4ɔ SURGICAL SPECIMENS

T l C y	N m b f C se St d d	N t	T t	Pos Res l Obta d by					
				SM	CU	CP	f CU	S f GP	CU GP
Th ll l		3	4	3	1	2	1	1	0
Th k ll d	6	1	11	7	7	7	5	3	4
O l l g	4	4	0	0	0	0	0	0	0
Ul r t o — l l l	6	4		0	1	2	0	0	1
h ll g t t h l a	2	1	1	0	1	0	0	0	0
T t l	4		18	10	10	11	6	4	5

SM d c te st d sm f sed m t CU c lt e o t fi l m d m GP g p g oculat

lining I oniazid had been given to 20 patients of this group and 3 had received only streptomycin (or dihydrostreptomy cin) and PAS

The character of a tuberculous cavity may be influenced

by artificial attempts at cavity closure such as pneumotho rax thoracoplasty pneumoperitoneum etc by the type of drug therapy and by the nature of the pre existing lesion such as tuberculoma Open healing is probably related to present day chemotherapy especially with isoniazid

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Incidence of Relapse Related to Duration of Chemotherapy after Cavity Ciosure

	S irg cal G oup			Conse G oup			Comb d G p		
Du son of dru mon h af cavi los re	<4	4-8	8+	<4	4-8	8+	<4	4-8	8+
N mber of case	13	16	13	12	17	6	25	33	39
Perso m h bserved nce ca y losu	91 5	311	125 5	2 6	377 5	267	517 5	638	39 5
R lapses	2	0	0	3	1	0	5	1	0
R lapse pe 100 pe son years	8 2	0	0	15 9	3 7	0	(01) 11 6	(- 5) 1 9	(1 54) 0
	3 3			5 9			4 7		

E pect d 1 p show p th f mb d g oup X t t how P betw 0 0 d 0 05

given to 92 patients 46 had major or minor surgery also The relation between duration of chemotherapy and relapse was studied (table) No statistical difference was noted between relapse rate in conservatively treated and that in surgically treated patients after chemotherapy was discontinued

Cavitation in pulmonary tuberculosis has long been re

(3) Th 11 1 9 M h 1956



Fig 41.—Specimen. Upper portion of left lung showing huge thin-walled cavity with smooth lining and several trabeculae coursing through it—striking example [illegible] (Courtesy of Thompson, J. R., Am. Rev. Tuberc. 7[illegible] 159 [illegible] August 1955.)

BACTERIOLOGIC DATA ON MATERIAL ASPIRATED FROM BRONCHIAL TREE OF 45 SURGICAL SPECIMENS

[illegible]	Specimens Studied	[illegible]	Pos	SM	CU	GP	SM CU	SM GP	CU GP
Th[illegible]		9	4	4	3		1	1	0
Th[illegible]	26	12	11	7	7		5	3	4
O[illegible]	4	4	0	0	0	0	0	0	0
[illegible]	8	4		0	1	2	0	0	1
[illegible]	^	1	1	0	1	0	0	0	0
Total	4		19	0	10	11	6	4	5

SM indicates stained smear; CU, culture on artificial medium; GP, guinea pig inoculation.

luring Isoniazid had been given to 20 patients of this group and 3 had received only streptomycin (or dihydrostreptomycin) and PAS

The character of a tuberculous cavity may be influenced

daily was definitely less effective in these groups. Advanced pulmonary tuberculosis responded better when isoniazid was included as one of the multiple drugs. Other studies failed to show that a three drug regimen was superior to either streptomycin isoniazid or streptomycin PAS.

Antimicrobial therapy for tuberculosis should include isoniazid. Whether isoniazid alone would be effective is unknown but it may be useful in early stages of the disease. Which second drug to use with isoniazid is unclear. Other

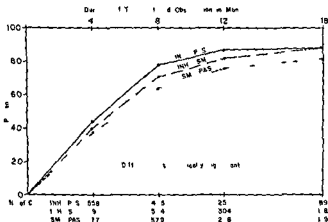


Fig 4 – Eff t f g m on re 1 f nf t ou n (Court f T k
W B nd L g D G Am R Tuber 72 756-78 D embe 1955)

studies have shown that isoniazid daily with streptomycin daily consistently produced the best results. Results in the present study were almost as good when isoniazid was combined with streptomycin twice weekly but isoniazid resistant strains of tubercle bacilli were more frequent. There was little indication whether streptomycin or PAS is preferable as a companion to isoniazid.

The criterion of roentgenographic improvement was of little value and more objective measures must be applied in analyzing therapy. Race and age were not clearly associated with outcome. The more advanced the disease and the larger the cavitary component the less satisfactory were the *re*

garded as gravely important with increasing emphasis in recent decades on closure or excision of the cavity Possibly the drugs now available may sterilize the cavity or indefinitely suppress bacterial activity This may modify the present emphasis on eradication of the cavity

With chemotherapy as the sole definitive treatment closure of tuberculous lung cavities may be expected in 50 79% of cases Among the 138 patients in whom cavities were closed under chemotherapy six relapses were observed The most important factor in determining the likelihood of relapse appeared to be duration of chemotherapy after cavity closure Size of the residual solid foci was not definitely related to incidence of relapse

• [In the last analysis it is on the basis of such careful clinical follow up studies as this rather than on pathologic and bacteriologic observations of re ec ed lesions valuable as the e may be that the indications for surgical resection in pulmonary tuberculosis may b st be formulated —Ed]

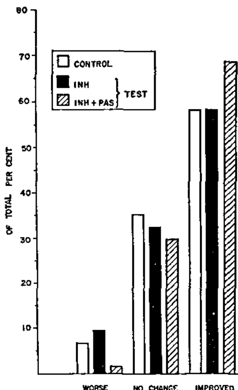
Isoniazid Streptomycin and Para Aminosalicylic Acid Compared as Two Drug Regimens in Treatment of Pulmonary Tuberculosis among Previously Untreated Patients III Account of Co operative Investigation of Veterans Administration Army and Navy August 1952 to September 1954 William B Tucker (Duke Univ) and Dorothy G Livings[4] (V A Washington D C) report on 2 187 patients randomly assigned to 300 mg isoniazid daily plus 12 Gm PAS daily 300 mg isoniazid daily plus 1 Gm streptomycin twice weekly or 1 Gm streptomycin twice weekly plus 12 Gm PAS daily The three groups and the extent of disease in each were comparable

No one treatment schedule was significantly better although streptomycin PAS was not quite as effective as the others The streptomycin PAS regimen was significantly less effective in reversing infectiousness (Fig 42) and cavities were closed at a significantly lower rate (Fig 43) No significant differences among the three treatment groups were apparent by roentgen examination

The three regimens were equally effective for minimal pulmonary tuberculosis but treatment with isoniazid PAS daily was more effective in advanced cases and in those with the largest cavities Streptomycin twice weekly with PAS

(4) Am R Tub rc 72 756-78 D embe 1955

PAS The length of the test period was three months The distribution of the patients in the three groups was determined by random allocation before chemotherapy was initiated Temperature erythrocyte sedimentation rate weight



F g 44—P t t l fi d ord g t oe tg ng ph h g (Court y f Th pe t T l C mm tt Sw d h N t l A oc t g t T be los A be aca di 30 165 194 1955)

differential count presence of acid fast bacilli in smears of sputum bacterial sensitivity and tests on circulatory liver and kidney functions were analyzed at regular intervals during the test period Pulmonary roentgenograms were taken each month

The effect of INH only or of the combination of INH and

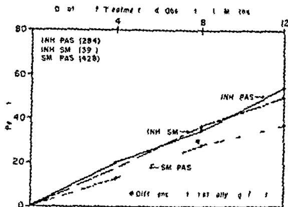


Fig 43 — Effect of regimen on cavity closure (life table method) without resectional surgery (Courtesy of Tucker W B and Living D G Am Rev Tuber 72 756-78 December 1955)

sults Bilateral involvement responded less than unilateral

Which antimicrobial therapy to prescribe will depend on variations in the disease Co operative investigations in the United States and Britain show that isoniazid is effective with either streptomycin or PAS and that a regimen of daily isoniazid and daily streptomycin consistently gives the best results

• [Dr Tucker and Mrs Livings do not include in this most thorough analysis of various two drug regimens a comparison of these with isoniazid alone They have in progress however a review of earlier data bearing on this point which may be of considerable importance relative to individualization of treatment and conservation of therapeutic resources The authors are notably careful and restrained in drawing conclusions They make the observation that the co operative studies of the antimicrobial therapy of pulmonary tuberculosis have not answered with final precision the question which regimen is best but have laid the basis with factual information for the practical clinical decision to be made by the well informed physician —Ed]

Isoniazid (INH) PAS and Streptomycin in Pulmonary Tuberculosis Control Study on 443 Cases was carried out by the Therapeutic Trials Committee of the Swedish National Association against Tuberculosis[5] One group of 218 patients served as controls Of these 188 were treated with a combination of PAS and streptomycin The others were given PAS only or PAS and thioacetazone (conteben®) A test group comprising 156 patients was given INH daily and a second test group of 69 patients a combination of INH and

(5) Act t berc scand nav 30 16 194 1955

INH only About half the strains of tubercle bacilli examined after three months of INH treatment were resistant to INH In patients receiving combined treatment with PAS and INH resistance of tubercle bacilli to INH did not develop during the observation period

Chemotherapy had to be discontinued in seven controls and in four patients in the test groups because of drug intolerance

• [The two test groups (viz INH and INH PAS) were not treated concurrently and the control group represents an amalgamation of two groups each of which was a signed concurrently to one of the test groups There were some variations in the treatment given to the control groups The second test group (INH PAS) was less than half as large as the first (INH) and it was established only after it was found in the fir t group that there was a considerable tendency to the development of drug resistance in vitro Nevertheless the claim that the comparison is statistically valid can probably be accepted and the combination of isoniazid with PAS shows some superiority over isoniazid alone Whether this is entirely due to prevention of isonia id re istance is perhaps not so certain as it may seem even though it is reported that no resistance to isoniazid developed in the INH PAS group during the observation period Three months is a relatively short time for this factor to result in demonstrable clinical disadvantages (see next article by Fox and Sutherland) An alternative explanation might be that PAS blocks the partial inactivation by acetylation of isoniazid Evidence of this has been reported by Mandel *et al* (Proc Soc Exper Biol & Med 91 409 1956) and also by Morse and hi associates (*Transactions of 15th Conference on Chemotherapy of Tuberculosis* U S Veterans Administration 1956 in press) —Ed]

Clinical Significance of Positive Cultures and Isoniazid Resistant Tubercle Bacilli during Treatment of Pulmonary Tuberculosis Report to Tuberculosis Chemotherapy Trials Committee of Medical Research Council Wallace Fox and Ian Sutherland[6] (London) studied 234 patients with pulmonary tuberculosis treated with isoniazid alone 100 mg twice daily for three months At the end of two months 91 had negative cultures 58 had strains sensitive to isoniazid 47 moderately resistant strains and 38 strongly resistant strains

Patients with marked pyrexia high sedimentation rates extensive cavitation and poor general condition had positive cultures at the end of two months more frequently than those with more favorable clinical characteristics at the beginning of therapy The emergence of isoniazid resistant organisms was related only to the extent of initial cavitation Clinical

(6) Th 10 85 98 J 1955

PAS was about the same as the effect observed in the control group on PAS and streptomycin therapy with respect to temperature erythrocyte sedimentation rate and differential count The gain in weight was more rapid in patients given INH only than in those given PAS and streptomycin or PAS and INH

On the basis of the roentgenographic change it became evident that PAS and streptomycin had about the same ef

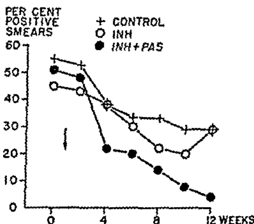


Fig 45 —Percentage of smears containing tubercle bacilli Arrow indicates beginning of chemotherapy (Courtesy of Therapeutic Trials Committee Swedish National Association against Tuberculosis Acta tuberc scandinav 30 105 194 1955)

fect as INH alone Combined INH treatment (INH and PAS) on the other hand gave better results than the two other forms of chemotherapy The difference was statistically significant (Fig 44)

The percentage of positive smears fell rapidly after the institution of chemotherapy from an initial value of about 50% There was no significant difference in effect between the combination of PAS and streptomycin and INH only Significantly lower values however were attained with combined INH therapy than with PAS and streptomycin or INH only (Fig 45) Grouping according to sex and to tuberculosis category showed the same trends

Bacterial resistance developed rapidly in patients given

closerine therapy for 10 12 months 15 had consistently negative sputums on smear and 6 on culture as well Sputums that remained positive had a reduced number of bacteria and occasionally a specimen was negative Thus cycloserine fills the need for an antimicrobial agent in patients who have failed to respond to other drugs especially if surgery is contraindicated

In the daily dose of 20 25 mg/kg for as long as 14 months cycloserine elicited few reactions Mild untoward symptoms disappeared even though the drug was continued

Man 32 had diffuse nodular pulmonary and hepatic tuberculosis which did not respond to streptomycin and isoniazid Cycloserine 1 Gm/day was begun and the other drugs discontinued Temperature became normal within five days weight was steadily gained and he became ambulatory within four weeks After 3/ months of treatment a repeat liver biopsy showed no tuberculosis and a chest x ray revealed complete clearing of the nodules An intractable hic cough developed unresponsive to medication and signs of diffuse brain involvement were present Left hemiplegia occurred and temperature spiked to 105 F Cycloserine was discontinued and streptomycin and isoniazid started He died seven months after admission to the hospital Autopsy revealed numerous tuberculomas of the brain with caseation and marked midbrain involvement

• [It appears that cycloserine will achieve a secure place in the l t of effective agents in the antimicrobial therapy of tuberculosis Whether it will stand in the front rank with isonia id and streptomycin or only with viomycin as a useful secondary defense is not yet clear The possible advantages of its administration concurrently with one or more of the other antituberculous drugs have yet to be evaluated McLean (Abstracts of papers annual meeting National Tuberculosis Association 1956) in a randomi ed comparison of cycloserine alone with ison azid PAS found cycloserine to be therapeutically significantly less effective Both minor and major convul ive sei ures occurred (20 in 229 patients) but these were relatively easily controlled by reduction in dosage and no permanent ill effects were reported —Ed]

Hinconstarch in Treatment of Pulmonary Tuberculosis Report on Pilot Investigation Vincent C Barry Michael L Conalty Henry E Counihan and Brendan O Brien[8] (Dublin) treated 12 patients none of whom had received previous antituberculosis therapy with hinconstarch a polymer prepared from periodate oxidized potato starch by condensation with equimolar proportions of isoniazid and para aminobenzalthiosemicarbazone The drug was administered orally in 100 and 200 mg capsules initially 0 5 Gm daily in

(8) Am R T be 73 19 2 8 F bru ry 1956

progress was little different at the end of three months between patients with resistant and patients with sensitive strains. Relatively poor clinical progress and the development of bacterial resistance may both be characteristics of patients with a particular host response or type of disease.

Clinical disadvantages due to isoniazid resistance are possible but were not definitely shown in this study. Nevertheless, the development of isoniazid resistance should still be considered as indicating some loss of clinical effectiveness and a potential risk to public health. Isoniazid should be given only in combination with suitable dosages of other drugs.

Treatment of Human Tuberculosis with Cycloserine: A Year's Progress is reported by Israel G. Epstein, K. G. S. Nair and Linn J. Boyd (New York). Preliminary animal experiments failed to corroborate the in vitro activity of cycloserine against virulent tubercle bacilli in mice, rats, guinea pigs, rabbits and monkeys. In man cycloserine is an effective and safe antituberculous antibiotic. This discrepancy is a paradox that casts serious doubt on routine in vivo animal testing of chemotherapeutic agents as reflecting what might be expected in man.

Cycloserine was given to 109 patients with various types of tuberculosis: 44 previously untreated, 62 with chronic isoniazid and streptomycin failures due to resistance and 3 with extrapulmonary lesions. In six patients both pulmonary and extrapulmonary lesions were present. Used alone the dose of cycloserine was 1.15 Gm./day.

Cycloserine alone has given results as satisfactory as those produced by other antimicrobial agents in previously untreated patients. After a year of continuous therapy in five patients, results were excellent. Fever was promptly reduced, weight gain was prompt and progressive with increased appetite and feeling of well being, and diminution in cough and reduction in sputum were striking. The bacillary content of the sputum was reduced and became negative on smear and culture.

Patients with chronic tuberculosis had become resistant to streptomycin and isoniazid and sputums were strongly positive for acid fast bacilli. Of 24 such patients given cy-

(7) Ant. & Ch. An. I. pp. 141-147, 1955-56.

dose series many patients had localized and temporary in creases in roentgenographic abnormalities of minor signif icance The increases were always reversed and no patient was roentgenologically worse at six months This phe nomenon may have been related to the chemotherapy per haps a provocative response to isoniazid or antagonism of its activity

All patients had sputum or gastric aspirates positive for Mycobacterium tuberculosis before therapy Dosage of 30 mg pyrazinamide/kg was definitely inferior to 50 mg / kg in reversing infectiousness three and six months after therapy was started Of the four patients in whom pyrazin amide was discontinued because of toxicity two had hepa titis indicating that reduction of dosage did not obviate hepatic toxicity Simple methods must be found for early de tection of hepatic damage Without such methods and with out criteria for identifying patients susceptible to pyrazin amide hepatitis the full dose 50 mg /kg should be used but only under carefully controlled conditions

• [The only reason for inclusion of this es entially negative and dis couraging report is to emphasize again the danger of this regimen and its unsuitabil ty for routine use Since this paper was published we have en countered another instance of severe hepatitis resulting in death of a patient who received 50 mg /kg /day of pyrazinamide despite carefully controlled conditions of close observation and frequent tests of hepatic function This case will be reported elsewhere in detail Phillips and Hor ton (Am Rev Tuberc 73 704 1956) also found the incidence and sever ity of hepatitis to be excessive and they also believe pyra inamide isonia id (pyrazinamide given in dosage of 750 mg four times daily) should not be used as a routine initial treatment regimen Fortunately no deaths occurred in their series of 32 patients but 2 had jaundice and 3 others had increased bromsulfalein retention The high incidence of hepatic toxicity in these relatively small series of patients is in contra t to the much lower incidence of this complication reported in several studies in volving larger numbers of patients The reasons for this difference are undetermined Pyraz namide appears still to have value in emergency situations as for instance in postoperative spreads in patients whose in fect ons are resistant or unresponsive to the other drugs in standard comb nations —Ed]

Hormone Therapy in Tuberculosis Use of Hypophysial Adrenal Hormones in Treatment of Tuberculosis Clinical Anatomopathologic and Experimental Study R Even Ch Sors (Paris) A Delaude (Toulouse) R Roujeau Y Trocme and G Commare[1] (Paris) report observations on 160 cases

(1) R tube P 19 1249 1302 1955

creased to 1 2 Gm and in some cases to 1 6 Gm in three divided doses

After three months of treatment general physical condition was unimproved in only one patient Appetite was good in all patients and only one did not gain weight Cough responded rapidly and in all but one patient cough and sputum completely disappeared Initially only two patients were febrile and both were afebrile by the end of the three month treatment The erythrocyte sedimentation rate improved in all patients and became normal in eight One had complete x ray clearing four marked improvement three moderate improvement and four slight improvement

The sputa from all patients before and during the early stages of therapy were consistently positive for tubercle bacilli By the end of the 12th week 10 of the 12 patients had negative cultures

The absence of significant toxic manifestations and the fact that therapeutic effects were comparable to those of the best chemotherapeutic agents in use suggest that lincon starch should have a definite place in chemotherapy of tuberculosis

Pyrazinamide Isoniazid in Tuberculosis III Observations with Reduced Dosage of Pyrazinamide are reported by Carl Muschenheim (New York Hosp Cornell Med Center) Avrum Organick Robert M McCune Jr John Batten Kurt Deuschle Ralph Tompsett and Walsh McDermott[9] (Navaho Med Center Fort Defiance Ariz) Daily 4 5 mg isoniazid/kg and 20 30 mg pyrazinamide/kg were administered to 61 patients for 12 13 weeks and then isoniazid alone was continued Previous higher doses of pyrazinamide had caused a high incidence of hepatic toxicity

Of 40 patients about whom data were available at the end of six months 32 were substantially improved 3 were not significantly changed and none was worse At 9 and 12 months the number of patients available for evaluation was insufficient Comparison with a previous study showed that substantial roentgenographic improvement occurred in the same proportion of patients (about 80%) whether the dose of pyrazinamide was 50 or 30 mg/kg However in the low

(9) Am Rev Tub c 72 851 855 D c mbe 1955

dose series many patients had localized and temporary increases in roentgenographic abnormalities of minor significance The increases were always reversed and no patient was roentgenologically worse at six months This phenomenon may have been related to the chemotherapy perhaps a provocative response to isoniazid or antagonism of its activity

All patients had sputum or gastric aspirates positive for Mycobacterium tuberculosis before therapy Dosage of 30 mg pyrazinamide/kg was definitely inferior to 50 mg/kg in reversing infectiousness three and six months after therapy was started Of the four patients in whom pyrazinamide was discontinued because of toxicity two had hepatitis indicating that reduction of dosage did not obviate hepatic toxicity Simple methods must be found for early detection of hepatic damage Without such methods and without criteria for identifying patients susceptible to pyrazinamide hepatitis the full dose 50 mg/kg should be used but only under carefully controlled conditions

• [The only reason for inclusion of this essentially negative and discouraging report is to emphasize again the danger of this regimen and its unsuitability for routine use Since this paper was published we have encountered another instance of severe hepatitis resulting in death of a patient who received 50 mg/kg/day of pyrazinamide despite carefully controlled conditions of close observation and frequent tests of hepatic function This case will be reported elsewhere in detail Phillips and Horton (Am Rev Tuberc 73 704 1956) also found the incidence and severity of hepatitis to be excessive and they also believe pyrazinamide isoniazid (pyrazinamide given in dosage of 750 mg four times daily) should not be used as a routine initial treatment regimen Fortunately no deaths occurred in their series of 32 patients but 2 had jaundice and 3 others had increased bromsulfalein retention The high incidence of hepatic toxicity in these relatively small series of patients is in contrast to the much lower incidence of this complication reported in several studies involving larger numbers of patients The reasons for this difference are undetermined Pyrazinamide appears still to have value in emergency situations as for instance in postoperative spreads in patients whose infections are resistant or unresponsive to the other drugs in standard combinations —Ed.]

Hormone Therapy in Tuberculosis Use of Hypophysial Adrenal Hormones in Treatment of Tuberculosis Clinical Anatomopathologic and Experimental Study R Even Ch Sors (Paris) A Delaude (Toulouse) R Roujeau Y Trocme and G Commare[1] (Paris) report observations on 160 cases

(1) R tuberc P 19 1249 130 1955

(104 of pulmonary tuberculosis) ACTH and cortisone in association with antibiotics (streptomycin and isoniazid) have a decisive effect on acute and progressive tuberculous inflammation Most satisfactory results were obtained in 54 cases of acute tuberculosis of serous membranes (mostly pleural) whatever the localization cure is attained rapidly with minimal sequelae Intravenous infusion of ACTH is the method of choice with local administration irritation caused by the



F g 46 (left) —La g cav ty of 6 p l be (Ap 1 19 1955)
F g 4 (ght) —D pp f ty (M 5 1955)
(C t y f E R t l R t b I 9 19 1249 1302 1955)

injections can cause extension of the lesion and increase complications

By the combined hormone and antibiotic therapy in pulmonary tuberculosis infiltrates and recent nodules may clear in three weeks Cavities either disappear (Figs 46 and 47) or undergo bullous transformation through pericavitary healing Afterward they are responsive to continued antibiotic treatment or amenable to collapse therapy and they heal with minimal sequelae Among patients with localized or extensive acute lesions there were 25 with nodules of whom 9 were cured and 12 improved Of 25 with infiltrated lesions 12 were cured and 11 improved Of 36 with cavities 14 were cured and 9 improved

Hormone therapy though less definitely indicated in chronic forms of the disease may be used in (1) chronic serous tuberculosis in which satisfactory results may be expected only with simultaneous local and general administration (2) pulmonary tuberculosis with intolerance to antibiotics and (3) severe tuberculosis in which the favorable effect on the general condition may aid in preparation of the patient for surgery

Cortisone 50 mg /day for about three weeks was used in eight cases four times after a course of ACTH and four times alone Radiologic improvement was obtained in two chronic cases resistant to antibiotics Most patients (86) were treated with intravenous infusions of ACTH most often in a single three week course Several patients with chronic tuberculosis received two or three courses repeated at three week intervals Total dosage in successful cases was 300 350 mg Better results were obtained in younger patients Average age of all patients with localized acute tuberculosis was 31 and of those who obtained good results 26 Similarly average age of those with extensive acute lesions was 38 and of those with good results 34

Anatomic study of 13 resected lungs indicated that ACTH and cortisone cause disappearance or notable diminution of nonspecific exudative lesions permitting full u e of antibiotics In pachypleuritis there is more rapid organization of exudates which cannot be resorbed

Statistical analysis confirmed the fact that ACTH and cortisone do not inhibit but reinforce the effect of antibiotics on experimental tuberculosis

• [This timely report on a large series of patients with tuberculosis of various types treated with steroid hormo es w ll surprise and may even hock many Amer can readers The results however appear to be good and the authors report no harmful effects All patients of course received the hormones n association *with effecti e antim crobial therapy* The princ pal ri k a possible enhancement of the infection were this primarily resistant to both ant microbial drugs used (streptomycin and ison a d) but thi r sk is probably remote The choice of ACTH as the preferred hormonal agent is soundly based and the apparent improvement of clinical re ults n acute processes over tho e attainable by antimicrobial therapy alone s consistent with the preponderance of experimental evidence an l some earl er clinical find gs (see 1953 54 YEAR BOOK pp 181 184 and 1954 55 YEAR BOOK pp 194 198)

Whether the indications for steroid hormone therapy in tuberculosis will ultimately be as broad as Dr Even and his associates here suggest must depend on further experience There are however in the same issue

of the *Revue de la tuberculose* several other reports of smaller series and these seem for the most part to confirm the present authors experience and to support their conclusions

There is still little in the American literature concerning the practical use of steroid hormone therapy in tuberculosis except for a few reports on tuberculous meningitis But in many clinical centers this treatment has been used in a few pulmonary cases usually as a desperate measure in acutely ill patients apparently not responding to isoniazid and streptomycin with usually promptly favorable and sometimes dramatically life saving results Despite this unqualified statements are still made that active tuberculosis is a *contraindication* to the use of steroid hormones whereas the *indications* in tuberculosis are rarely discussed or even recognized —Ed]

Tuberculin Hypersensitivity in Tuberculous Infants Treated with Isoniazid is reported by Arthur Robinson Maryethel Meyer and Gardner Middlebrook (Denver) in four patients under age 2 with positive Mantoux reactions to 1 1 000 dilution on contact examination and normal chest x rays They were all treated with 8 mg isoniazid/kg body weight/day In all patients reaction became negative to old tuberculin in 1 100 dilution A second group of two patients clinically similar to the first group were still sensitive to old tuberculin in 1 1 000 dilution at the end of five and six months of therapy In a third group of seven patients—all with positive reactions to old tuberculin and abnormal findings in chest x rays—reaction remained positive to a dilution of 1 1 000 despite at least seven months of isoniazid at the same dosage level

Since the use of antituberculous drugs decrease in skin hypersensitivity to tuberculin has been noted in laboratory animals during or after treatment with either streptomycin or isoniazid However it has not previously been reported that in tuberculous human beings treated with antimicrobial agents skin reaction became negative to 1 mg old tuberculin as in four of these patients

Studies on Isoniazid Resistant Strains of Mycobacterium Tuberculosis II Virulence for Mice and Guinea Pigs and Growth Pattern (Cording) in Vitro of Strains Resistant to 100 Micrograms of Isoniazid per Milliliter Studies have shown that tubercle bacilli resistant to isoniazid have modified virulence for guinea pigs In the first weeks after infection isoniazid resistant bacilli produce progressive lesions

(2) N w E gland J M d 25 983 985 J ne 9 1955

as do drug susceptible bacilli but lesions due to resistant bacilli regress in later weeks Reports differ on the virulence of isoniazid resistant strains for mice Some authors have reported isoniazid resistant strains to be a virulent for mice as the parent drug susceptible strains while others have found such resistant strains to be of low virulence A relation has been suggested between the degree of isoniazid resistance of the bacilli and their virulence for mice and guinea pigs and between their catalase activity and their virulence for guinea pigs

Michael L Conalty and Ethna L Gaffney[3] (Dublin) observed the virulence for mice and guinea pigs of eight isoniazid resistant catalase negative strains of M tuberculosis the growth requirements of which were studied at time of inoculation together with bacillary growth pattern in a Proskauer and Beck type medium The study showed that four of the eight strains were fully virulent for mice and that these same strains were also the most pathogenic for guinea pigs though all strains exhibited attenuation of virulence in guinea pigs However death from tuberculosis occurred in guinea pigs infected with one highly resistant strain during initial advance of the disease With another strain death occurred in a much later second period of advance after a period of regression Other strains showed only low virulence as assessed at the end of 200 days One of the resistant strains a variant of H37Rv failed to immunize mice against subsequent virulent infection

Except for one of dubious identity all these drug resistant strain of M tuberculosis showed well marked cord formation in vitro Were it the cord factor which determined virulence unaltered virulence would be expected for both mice and guinea pigs or assuming some change in the nature of the factor decreased virulence for both Thus the importance of the cord factor in determining virulence seems to be doubtful

(3) Am R Tb 71 799 809 J 1955

Reversal of Pulmonary Hypertrophic Osteoarthropathy by Vagotomy is reported by Geoffrey Flavell[4] (London). A number of patients with inoperable bronchial carcinoma and hypertrophic osteoarthropathy have had thoracotomy to clear the hilus and divide the pleural investment and all the fibers of the vagus or sympathetic entering the root of the lung. In these patients joint pains were relieved as effectively as in others treated by pulmonary resection. In two patients with clubbing and arthralgia, exploratory thoracotomy alone had no effect.

In five patients division of the vagus alone was effective. In two of these the branches of the vagus entering the hilus on the affected side were cut, with immediate and complete relief from joint symptoms and resolution of effusions. In the other three the vagus was isolated and cut as far as possible from the hilus. *Equally dramatic relief was obtained* with disappearance of joint swelling.

It would seem, therefore, that manifestations of pulmonary hypertrophic osteoarthropathy are caused by a neural reflex passing from the affected lung in the fibers of the vagus nerve and can be terminated by severing the vagus even when the related growth is irremovable.

* [*This remarkable observation has not, to my knowledge, been made before. Nor have any of the theories advanced concerning the pathogenesis of this disorder appeared to be as tenable.*—Ed.]

Noninfluenzal Viral Infections of Respiratory Tract are reviewed by John H. Dingle and A. E. Feller[5] (Western Reserve Univ.). Acute respiratory disease was the name given to a grippelike infection that occurs epidemically in winter months in recruits and not in seasoned service men. Immunity follows the infection. Hospitalized patients are acutely ill with fever, chilliness, malaise, anorexia, irritated throat, hoarseness and cough. They have *moderate pharyngeal injection*, pharyngeal lymphoid hyperplasia and minimal cervical adenopathy. Acute illness lasts three to seven days.

(4) Lancet 1:260-262, Feb. 11, 1956.
(5) New England J. Med. 254:465-471, Mar. 8, 1956.

with one or two weeks of convalescence The disease could be transmitted by filtered secretions When the RI-67 virus was isolated an antibody rise to this virus could be demonstrated in many cases diagnosed as acute respiratory disease but not in those diagnosed as common cold or primary atypical pneumonia At least two types of this new respiratory tract virus types 4 and 7 can cause acute respiratory disease of recruits The disease has not yet been recognized in civilians Treatment is symptomatic and supportive Work is in progress to develop the RI 67 virus as a vaccine

Cases of pharyngitis and tonsillitis not associated with bacteria usually are mild and of short duration lasting about five days The onset of fever headache and anorexia is gradual Sore throat hoarseness and cough are usually present nasal symptoms are not prominent The palate pharyngeal wall and tonsils are injected with or without exudate Cervical lymphadenopathy may be present and the lungs are occasionally involved The white blood cell count is usually below 10,000 and peak temperature between 101 and 102 F with temperature decline by lysis The cause is unknown probably some forms are due to the newly discovered respiratory tract viruses Type 3 virus has occurred in children in the summer with clinical symptoms of fever constitutional symptoms mild pharyngitis occasional rhinitis and exudate cervical lymphadenopathy and conjunctivitis Antibodies to types 1 and 2 agents are common in children

Primary atypical pneumonia studied extensively since World War II is of undetermined etiology It is an acute respiratory disease characterized by a gradual onset of constitutional symptoms cough sputum pulmonary infiltration and prolonged convalescence The diagnosis is generally by exclusion of known agents Cold agglutination and streptococcus MG agglutination help confirm the diagnosis Since bacteria free secretions can transmit the disease in man presumably it is of viral origin Probably more than one unidentified agent may produce the syndrome and the same agent or agents may induce both a pneumonic and a non pneumonic form Sulfonamide drugs and penicillin are not beneficial and the specific effect of broad spectrum antibiotics is controversial

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The common cold is transmissible from one human being to another by intranasal inoculation of bacteria free respiratory tract secretions It is assumed to be a viral disease but the agent has not been cultivated or identified Laboratory confirmation is not possible and there is no agreement on criteria for clinical diagnosis Differential diagnosis includes hay fever perennial allergic rhinitis irritation due to dust and vasomotor and other changes Exclusion of these causes is often impossible The newly isolated respiratory viral agents are not present in secretions from the common cold antibodies to the known types of virus do not increase in titer in the convalescent phase serums and inoculation of volunteers with these agents produces illnesses that do not resemble the common cold clinically

• [This important Medical Progress report should be read in the original especially by those unfamiliar with the background data and the relation of recently discovered viruses to previously described clinical syndromes —Ed]

Anomalous Pulmonary Arteries and Cystic Disease of the Lung Edgar P Mannix Jr and Cameron Haight[6] (Univ of Michigan) observed this condition in 15 patients (6 males) aged 2 34 during intrathoracic operations between 1939 and 1951

The anomalous artery usually arises from the thoracic or the abdominal aorta or certain of its branches and the most common site of origin is the descending thoracic aorta superior to the hemidiaphragm and in relation to the inferior pulmonary ligament The lung parenchyma supplied by the anomalous artery may be normal or may show congenital ✓malformations acquired morbid lesions or both

Symptoms were typical of chronically recurring suppurative disease of the lung Productive cough and chest pain were the most common complaints other symptoms included hemoptysis chills fever loss of weight and dyspnea Dulness to percussion and fine râles were common findings Clubbing of the fingers was found in only three patients No abnormalities were noted during bronchoscopy except signs of bronchitis

Differential diagnosis by x ray examination should include lung abscess empyema tension pneumothorax sup

(6) M d n 34 193 231 M y 1955

purative pneumonitis cystic bronchiectasis and pulmonary cyst The diagnosis of lung abscess must be guarded against since drainage of an infected congenital pulmonary cyst will not result in cure Bronchograms made in eight patients



Fig 48 —Cont t m d m j ted t mal s t y f ly ft m l f] f d mon t t m t on betw en m l d b h l (C t y t M x E P J d Il ght C M d e 34 193 231 M y 1955)

showed unsatisfactory filling of part of the involved lobe in six and no lipiodol® reaching the obviously demonstrable cavitation in four

Failure to appreciate the incidence with which anomalous arteries are associated with cystic pulmonary lesions may

lead to troublesome bleeding during drainage procedures or even fatal hemorrhage (In 11 patients, the anomalous artery was discovered identified and ligated before transection) An anomalous pulmonary artery should be suspected in any patient who had symptoms early in life and who has cystic dis



Fig 49—C o ect of l ft low l be show g m lt cy t c l on in poste o of t s a pect a l e th t (a row) l g w thi lumen f nom lou v s l (Court ey f M n x E P J nd H ight C M d ci e 34 193 31 May 195)

ease of the lung particularly of the lower lobes The only satisfactory treatment is resection of the involved portion of the lung

The entity is well demonstrated by the following case

Man 23 was hospitalized due to severe cough productive of ¼ cup purulent sputum daily for two years following a series of colds Physical examination showed crepitant rales diminished voice sounds diminished tactile fremitus at the left base and clubbing of fingers and toes Chest x rays revealed patchy pneumonitis of left

base Bronchograms showed poor filling of multiple cystlike cavities in left lower lobe

At surgery in the costovertebral gutter the lung was found to be attached to the aorta by a pedicle about 1 × 2 cm thick and 3-4 cm long Dissection of this pedicle revealed a large anomalous artery as thick as the radial artery coming from the aorta The anomalous artery was doubly ligated with silk and divided and left lower lobectomy and lingulectomy were performed (Figs 48 and 49) Convalescence was uneventful

Cavitation in Bland Infarcts of the Lung is reported in five men aged 48 80 by Lawrence R Coke and John C Dundee[7] (Winnipeg Man) Cavitation was seen by x ray in three of them about 20 days after infarction in one 58 days after and in the fifth 8 days after the second of two clinical infarctions All patients showed premonitory signs of tissue breakdown in the infarcted area such as intractability of cardiac failure persistence of fever or of increased pulse rate or both leukocytosis or raised erythrocyte sedimentation rate or both and less well defined symptoms of a continuing malaise such as anxiety apprehension anorexia and sweating

The value of anticoagulant therapy which should be continued until the patient is bedridden seems to be borne out by the present series In the first patient dicumarol® therapy was interrupted because it was thought that he had recovered from one infarction another followed almost immediately and progressed to abscess formation The second and third patients received anticoagulants throughout the illness despite repeated hemoptysis in the second patient both eventually made good recovery The fourth had no anticoagulants he died after attempts to drain the abscess by surgery The fifth patient with lung abscess was maintained on therapeutic prothrombin levels until he became ambulant though surgical drainage was considered but rejected because dicumarol® therapy would have had to be discontinued

Antibiotics were given as adjuvants but the authors believe that the main point in treatment is maintenance of impaired clotting power in the blood throughout the period of bed rest On this regimen even large abscesses healed well

(7) C d. M A J 72 907 910 J 15 1955

Chronic Massive Pulmonary Artery Thrombosis Alfred Ring and Jens R Bakke[8] in a review of 11 511 consecutive autopsies at the Queens General and Triboro hospitals in New York found massive pulmonary artery thrombosis in 21 patients 12 male and 9 female aged 15 months to 89 years (table)

Clinically pulmonary thrombosis is often masked by the underlying and complicating lesions of the lungs or heart but certain features are distinctive Dyspnea is usually the outstanding symptom and is out of proportion to the underlying disease In this series it was generally progressive and refractory to treatment The pulmonary fields may be relatively clear with little evidence of congestion despite widespread evidence of heart failure Cyanosis is usually prominent Cough and thoracic or epigastric distress may be present along with restlessness and mental confusion due to relative cerebral anoxia Most patients show evidence of right heart hypertrophy with subsequent right heart failure due to cor pulmonale

Though the diagnosis is difficult x ray angiocardiography and cardiac catheterization should help An abnormal hilar mass the enlarged pulmonary artery may be seen on x ray lung fields appear abnormally radiable and vascular markings decreased On fluoroscopy hilar pulsations may be absent on the involved side Angiocardiography often confirms pulmonary obstruction when massive thrombosis is present Cardiac catheterization usually reveals high right ventricular pressure and low cardiac output

Chronic thrombosis of the main pulmonary artery or the right or left main branch is relatively rare and is more apt to occur in the later decades of life although an infant aged 15 months had this complication with a tetralogy of Fallot According to most investigators most cases of pulmonary thrombosis are due to superimposition on a previous embolus

Despite massive thrombosis there was little evidence of massive infarction probably because of anastomoses between pulmonary and bronchial arteries In only 7 of the 21 patients was there evidence of pulmonary infarction and in

(8) Ann Int Med 43 781 806 Oct 1955

DATA IN 21 CA ES OF MASSIVE PULMONARY ARTERY THROMBOSIS

C se N	Se	A	M P lm A l d	I lm l se se	A P I l M	H	Ot Tl mbo Tl m	O m ll m	A ld l F
1	M	26	R ght l l ft	B l t l f d cd T B	t l v t be l	C p l l	M f t ght l g	M k d dy p	
2	M	50	R ght d l ft	P l t d se fil os phy d b h ect	Ch p l y d M t l f	R ght d l ft h pe t phy	Mese t c th mb l d pl c t l h l o	Dy p y	Cy l pe pa t f b dy sec d y p ly th m l t c t t pl l y l l a
3	M	70	M t k d ght	P l y fib t p	B h p m	C p l l	Th mb ght l ppe d g	I g dy p	P lmo ry te oscl
4	F	89	R ght d left	A t p	A t scl t h t d se	I ft t c l hy pe t phy	N	D dy p	
5	F	48	l ght	P l v t be los f d d	P l y t be l ge t h t f l	C p l l d l l t t f ll ch b	M l th m b ght l l p l g Th mb l ft m t	Dy p y	
6	M	62	R ght	C ght l g h p l y f t	B hog c c	R ght he t l l t t	B ll l th mb l ft l	Dy p a gh l a	
7	M	31	R ght	M l y t l l	l g d m t d p y t be l	L ft t l h pe t ply d ght t l d l t t	I f t ght l r l t	Dy p h t p y	P b e l l th A p l mc y t t

DATA IN 21 CASES OF MASSIVE PULMONARY ARTERY THROMBOSIS (*cont*)

Case No.	Sex	Age	Main Pulmonary Artery Involved	Pulmonary Disease	Associated [illegible] Diagnosis	Heart	Other Thromboembolic Phenomena	Outstanding Symptoms	Additional Features
8	F	57	Left	Pulmonary fibrosis and emphysema	Chronic lung disease. Congestive failure	Cor pulmonale and left ventricular hypertrophy	Infarct left lower lobe. Thrombosis right auricular appendage	Dyspnea, cyanosis	Widely dilated pulmonary artery and loud pulmonic diastolic murmur
9	F	78	Right	Congestion and edema	Adenocarcinoma of duodenum	Right heart dilatation. Left ventricular hypertrophy	None	Abdominal pain	Metastases to omentum and peritoneum
10	F	46	Left	Pulmonary tuberculosis, far advanced	Pulmonary tuberculosis	No abnormality	None	Marked dyspnea	
11	F	82	Right	Lung abscess, infarction right	Lung abscess	No significant abnormality	Thrombophlebitis right leg and femoral vein. Pulmonary emboli and infarct	Chest pain	
12	M	56	Right and left	Pulmonary tuberculosis, far advanced	Pulmonary tuberculosis	Cor pulmonale	None	Marked dyspnea	Pulmonary [illegible] marked
13	M	66	Left	Lung cyst, right; tuberculosis, far advanced left	Pulmonary tuberculosis	No significant abnormality	None	Marked dyspnea	Continuous hospitalization for over 10 years. [illegible]
14	F	59	Right	Metastatic carcinoma	Disseminated [illegible]	No significant abnormality	Multiple pulmonary emboli	Dyspnea, [illegible]	Widespread metastases

DATA IN 21 CASES OF MASSIVE PULMONARY ARTERY THROMBOSIS (cont.)

Case No.	Sex	Age	Main Pulm. Art. Involved	Pulmonary Disease	Assoc. [illegible] Disease	[illegible]	Other Thrombo-embolism	Other [illegible]	[illegible]
15	M	58	Right	B h ect p lm y fibros d emphysem	Same	C p lm l d l ft t l hype t phy	P p l y mbol (l cal)	P g es e dy p cy	EKG h ge f he t sec d y p cly yth m m ked
16	M	81	Right	P lm y d	C ry oc l	Myoc d l f t	C ry th b t bol d f t ght l l be	Ch t p h ck	C n y scl
17	M	52	M n t k ght d l ft	P lm y t berc l f d a d	P l y t t rc l	Hype t phy f l ft t l d p lm y	N	Dy p a	M ked m d l h ft
18	M	15 mo th	Right d l ft	B o h p m	T t logy f F ll t	T t l gy f F ll t	N	D p d y	Y gest ca d
19	F	67	Right d l ft	N e	M p l m y th om b hype t e h t d e se	Hype t phy f b th t l d l t t f ght	Th mb phle-bit f b th l g d l c	Dy p	
20	F	78	Left	Sm ll pe ph l f rct	A t oscl t h rt d se	L ft t l hype t phy	Segm t l f rct f t l g th mb l ft l appe d g	M t l c f	Ge l d t al os
21	M	78	Right d l ft	Emphy m b h ecta RLL b ho-p m d f rct	M p l m y mbo-l d th m bos	L ft t l r hype t phy ght h t hy pe t phy p l m ary d l t t	I f t RLL th b ght t d t y d l ft popl t l	Dy p a	Th mb phl b t l ft leg mbol th pe mposed th b l

each the infarction was less than lobar in extent Anasto motic channels between bronchial arteries and the pulmonary artery have been shown to expand rapidly after experimental ligation of the pulmonary artery

The terminal clinical picture was that of failing cor pul monale In several instances the clinical diagnosis of cor pulmonale was made without recognition of the underlying pulmonary thrombosis

Pulmonary Lesions in Rheumatoid Disease with Re marks on Diffuse Interstitial Pulmonary Fibrosis According to Eli H Rubin[9] (Montefiore Hosp New York) rheumatoid disease is more descriptive than the term rheumatoid arthritis since other parts of the body besides the locomotor system are affected The pulmonary lesions are manifestations of the same disturbance and may simu late acute atypical pneumonia acute rheumatic pneumonia or acute diffuse interstitial pulmonary fibrosis Many pa tients have a history of allergy

In most patients joint symptoms antedate pulmonary manifestations and occasionally the latter appear as joint symptoms subside At times a nondescript pneumonia or pleurisy precedes joint symptoms for a brief period A pleural friction rub is frequently heard and biopsy reveals fibrinous dense pleural adhesions Chest x rays reveal small serous effusions but if taken serially should show remis sions and exacerbations Bilateral symmetrical abnormal lung markings are seen which represent interstitial paren chymal changes due to the underlying disease They may simulate tuberculosis sarcoidosis inhalation dust disease or viral or bacterial pneumonia

The lesions are similar to those of rheumatic pneumonia Pleurisy is frequent in both conditions Rheumatic pneu monia is as much an integral part of rheumatic fever as the articular cardiac and other visceral involvement Rheu matic and virus pneumonias have in common a hilar mem brane mononuclear cell infiltration nonbacterial exudate capillary engorgement and interstitial edema A small pro portion of patients with condition diagnosed as virus infec

(9) Am J Med 19 569 582 O t b 19 5

tion may actually have rheumatic pneumonia without other manifestations

Diffuse interstitial pulmonary fibrosis of unknown etiology may be due to a primary atypical pneumonia that has failed to resolve and has organized X ray and pathologic changes are indistinguishable from those of rheumatoid disease or from the interstitial pulmonary fibrosis described by Hamman and Rich Several patients have been described with severe prolonged bronchopneumonia associated with migratory polyarthritis erythematous skin eruptions slight splenomegaly jaundice gross hematuria fibrinous pericarditis and encephalitis Probably these changes represent a diffuse vascular disease

Idiopathic Pulmonary Hemosiderosis J R Browning and John D Houghton[1] report on three patients aged 18 22 and 24 at onset of symptoms Two died of the disease and one is in complete remission at age 30 The family histories were noncontributory and there was no history of toxin exposure The initial symptom was cough followed shortly by hemoptysis

The pathogenesis of this disease is unknown Characteristically the course is one of remissions and exacerbations In two patients x rays were completely clear during remission Acute episodes were characterized by severe cough massive hemoptysis and shortness of breath Areas of dullness rales and bronchial breathing could be detected and cyanosis was often present During severe attacks fever anemia and abnormal x rays were constant findings Results of all bleeding and clotting studies were normal

The two deaths occurred within five days of onset of symptoms of acute exacerbation and both were due to respiratory failure Transfusions may have helped one patient whose last exacerbation was prolonged and who went into remission after ACTH and cortisone therapy Remission may or may not have been due to these drugs

The diagnosis should be considered in persons with unexplained diffuse pulmonary infiltrations and anemia Cough with hemoptysis dyspnea fever and reticulocytosis are further evidence in favor of the diagnosis Demonstration of

(1) Am J Med 20 374 38 March 1956

hemosiderin containing macrophages is strong confirmation if the patient is free from heart disease If the patient is acutely and severely ill jaundice may be present Similar attacks may have occurred previously and if present long right sided failure may be seen Other causes of pulmonary hemosiderosis such as mitral stenosis, infectious processes and blood dyscrasias must be excluded

• [Prior to this report only 3 of a total of 33 cases reported in the English language in adults were known Two other single case report have been recently seen one in a boy aged 19 (Hamer Brit M J 1 1008 Apr 23 1955) the other in a boy aged 15 (Gluck Acta path et microbiol scandinav 37 241 1955) —Ed]

Pulmonary Alveolar Microlithiasis or Calcinosis of Lungs a rare and extraordinary disease in which microscopic stones are found within the pulmonary alveoli is reported by Theodore L Badger Leonard Gottlieb and Edward A Gaensler* (Harvard Med School) in the third case to appear in the English literature

Man 45 when first seen nine years previously had abnormal pulmonary shadows on routine chest x ray but was asymptomatic He had history of pneumonia but work and general histories were non contributory Results of physical and laboratory examinations were negative Six years later at age 42 interim history was uneventful except for definite increase in shortness of breath some weakness after exertion sporadic coughing and stringy colorless mucoid sputum Physical examination revealed fine scattered rales posteriorly but laboratory findings were negative Chest film demonstrated some increased density and extension

At age 43 a large stone was removed from the left kidney Cough became worse and sputum was abundant Results of bronchoscopy cytology bronchial washings pulmonary function and ventilatory studies were negative X ray disclosed emphysematous blebs at both apexes Resting al eolar arterial oxygen difference was 34 mm Hg four times normal accounting for extreme physical incapacity on slightest exertion Weight loss was progressive Another large left ureteral tone was removed and he continued passing small stones and gravel Cortisone ACTH urethane and a low oxalate diet were without benefit

Metabolic studies revealed normal levels of calcium phosphorus serum proteins alkaline phosphatase nonprotein nitrogen and serum chloride Serum carbon dioxide level was slightly low Analysis of kidney stone revealed 60% ash no phosphorus uric acid or cystine and more than 4% oxalate

Weakness and dyspnea progressively increased and he was unable to drive a car because of the exertion He lost 24 lb in a year

(*) New England J M d 253 09 715 Oct 27 195

finger clubbing became marked and cyanosis appeared at rest He died in sleep

Autopsy revealed pleural cavities obliterated by dense fibrous adhesion enlarged right ventricle and many pebbles in the kidneys The lungs weighed 1 800 and 1 500 Gm and did not collapse outside



Fig 50 —C s-ect f ght l g t flec on f l ght f m m 1 th (C rt y f B dg T L t l N w E gl d J M l 53 709 715 O t 27 1955)

the chest cage Multiple minute calcific plaques were scattered over the surfaces Lobes were firm and without crepitus Apexes were large empty cavities traversed by thick fibrous trabeculae containing blood vessels (Fig 50)

Microscopically most alveoli contained concretions Interalveolar fibrosis was marked and the microliths were encircled by giant cells

progression The third stage appears to have the same clinical characteristics in all groups and is unremitting The cases of uncertain etiology are generally first recognized in this stage Dyspnea progresses and there are cough and expectoration of blood stained sputum Cyanosis is conspicuous There may be fever generally of low grade In this stage chest x rays may simulate miliary tuberculosis

Man 38 was exposed to explosion of flasks containing red fuming



Fig 52 (left)—C t urfa of Fo mal n fixed block sh wing v al nod l s m many f wh ch th t ro b l l m n can be d t f ed ×2
Fig 53 (ght)—Typ l l s on of b chial obl t ran show ng polypo d p peara f oc l d g ma H m t xyl
(C t sy J M Adam A J J Am J Med 19 314 32 \ g t 1955)

nitric acid After the accident he had cough and fever set in three weeks later Soon retrosternal pain tightness in the chest and shortness of breath developed On hospitalization he had a dry hacking cough dyspnea and a respiratory rate of 52/minute Temperature was 100 4 F pulse 128/minute and blood pressure 170/90 mm Hg *Abnormal findings were limited to wheezing and rales throughout* the chest The urine and hemogram were normal Chest film revealed small irregular densities 1 2 mm in diameter diffusely scattered throughout the lung fields Cyanosis increased respiration became shallow blood pressure fell and he died 28 days after exposure to nitric acid fumes

At autopsy the tracheobronchial tree was injected throughout and contained tenacious purulent material Lungs were markedly edematous and nodular on palpation The cut surface of Formalin fixed tissue blocks revealed the character of these nodules (Fig 52) Histologically all sections of the lung showed marked edema and many

focal areas of hemorrhage The characteristic lesion involved the bronchioles (Fig 53) The lumen was virtually obliterated by organizing exudate which often projected in a polypoid fashion The entire tracheobronchial tree was evidently involved at some stage

The term bronchiolitis obliterans should be used only when the process is widespread Similar lesions occurring as focal phenomena in many organizing processes are often purely morphologic findings without clinical correlation and frequently not obliterating lesions but early fibroblastic proliferation

Poisoning by inhalation of irritant substances in particular fumes of oxides of nitrogen is not uncommon and in the past has accounted for the larger number of cases of bronchiolitis obliterans Acute (pulmonary edema) rather than delayed fatalities are the rule

Chest Disease in Patients with Agammaglobulinemia Patients with this disorder have increased susceptibility to bacterial infection no gamma globulin in the serum no antibodies in blood or tissues and no immunologic response to antigenic stimulation The primary defect is in the formation of plasma cells due to disturbed hemopoietic reticulum function According to Robert A Good and William F Mazzitello (Univ of Minnesota) the usual presenting complaint is recurrent pulmonary infections with bronchiectasis empyema lung abscess atelectasis or pulmonary fibrosis

Agammaglobulinemia has been recognized in three forms the childhood form appearing only in males and transmitted as a sex linked recessive the adult form occurring in either sex at any age and the infant form appearing transiently during the first six months of life Of the 43 cases reported in the literature 24 were of the congenital and 19 of the acquired type The most consistent clinical finding is recurrent bacterial respiratory infection usually lobar or bronchopneumonia Bronchiectasis occurred in four of the congenital and four of the acquired cases

In children injections of gamma globulin 0 1 Gm /kg intramuscularly are beneficial With this replacement therapy circulating gamma globulin approaches 100 mg /100 ml which is protective against many common bacterial in

(5) D Ch t 29 9 35 J ry 1956

fections Injections must be given every three or four weeks Prophylactic antibiotic and gamma globulin therapy may ultimately prove to be the best therapy

Chest physicians are likely to be the first to encounter patients with agammaglobulinemia Early diagnosis and therapy *minimize the symptoms and may prevent destruction* of pulmonary parenchyma *due to recurrent severe bacte*rial disease

Pneumocystis Infection and Cytomegaly of Lungs in Newborn and Adult are described by H Hamperl[6] (Bonn Univ) In the newborn the disease most frequently occurs between the 10th and 14th weeks primarily in premature or

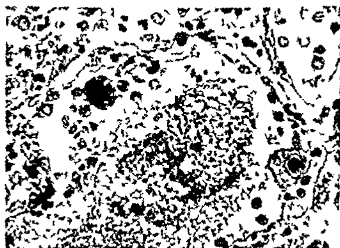


Fig 54—Tw cyt m g l ll t l l pt m t l m (al) lu filled by onal m t of p umocyt M t ch me sta d d l × 00 (Court y of H mpe l H Am J Path 3 1 13 J n F b 1956)

mature dystrophic infants Etiology is a parasite Pneumocystis carinii a protozoa or perhaps a fungus Incubation period is six weeks Mortality is between 30 and 40% The parasites are seen in lung smears bronchial secretions and histologic slides At autopsy all the lobes are consolidated homogeneous gray white *Plasmacytic infiltration of alveolar septa is extensive* and the alveolar lumens contain edema

(6) Am J P th 3 1 13 J F b 1956

fluid or a peculiar foamy material which is the parasite In infants interstitial plasmacytic pneumonitis is frequently associated with cytomegalic disease

In adults cytomegaly of the lungs may occur without pneumocystis pneumonitis and pneumocystis infection may exist without cytomegaly When lung tissue from a patient previously reported as having cytomegalic inclusion pneumonitis was reviewed protein coagula were found in the center of the alveoli surrounded by lighter staining borders of numerous round vesicles or honeycombs (Fig 54) Parasites identical with those found in infantile interstitial plasmacytic pneumonitis were therefore probably present Similar findings were present in another case

Cytomegalic virus alone probably does not cause pneumonitis In the cases reported simultaneous infection with P carinii was discovered This parasite causes interstitial plasmacytic pneumonitis in the newborn

Diagnosis of Intrathoracic Meningocele according to Heino Laitinen and Martti Turunen (Univ Clinic Helsinki) is usually not made preoperatively The condition is often accompanied by Recklinghausen s cutaneous neurofibromatosis and characteristic skeletal changes

In the past two years two patients with intrathoracic meningocele were treated at the Clinic In one the diagnosis was confirmed preoperatively by air myelography

Man 56 as long as he could remember had had reddish nodules and brownish patches on the skin After age 20 he became aware of increasing spinal deformity For the past 10 years he had had breathlessness and cough particularly on effort There had also been back pain between the shoulder blades on exertion Chest films eight years before revealed an intrathoracic tumor interpreted as benign

Examination showed reddish nodules in skin up to the size of a cherry and cafe au lait patches scattered over the trunk head arms and thigh Kyphoscoliosis of the thoracic spine was noted shown on x ray to be due to wedging of the 7th and 8th thoracic vertebrae The left pedicles of the 7th and 8th vertebrae were completely destroyed and the left intervertebral foramens formed one large opening A rounded well circumscribed homogeneous tumor measuring 10 × 8 cm was seen in the posterior mediastinum left of the spine at the level of the 6th to the 9th thoracic vertebrae (Fig 55)

Myelography was carried out 60 cc cerebrospinal fluid was withdrawn and replaced by air With the patient lying on the right side

( ) D s Ch t 7 547 552 M y 1955

and the upper part of the trunk lifted up the air was seen to rise into the saclike tumor of the thoracic cavity and form a semilunar air bubble along its upper contour (Fig 56) The location of the air bubble varied according to the patient s posture When he lay on the left side the air returned to the subarachnoid space Later the presence of air could be established in the enlarged ventricles of the brain

The tumor was approached through the bed of the resected 5th rib and a thin walled cyst the size of a tennis ball was detached from



Fig 55 Fig 56
(C tesy f La t nen H d T u e M D Ch t 27 547 55 M y 1955)

its surroundings It communicated with the spinal canal through a pedicle the lumen of which was passable by a finger The meningocele was excised and the resultant dural opening closed by dural and pleural flaps Convalescence was uneventful

Histologically the wall of the cyst consisted mainly of proliferative arachnoidea Some thinned dura could also be seen

The fact that the patient reported having had the cutaneous lesions of neurofibromatosis since early childhood but not having noted the progressive spinal deformity until his 20 s suggests that the primary disease was neurofibromatosis The extensive erosions of the posterior vertebral surfaces and of the pedicles which had produced dilatation of the spinal canal suggested a disease of the dura which made it too weak to resist the pressure in the subarachnoid space The protrusion of the saclike dilatation of the intraspinal meninges seems to have been a later process

Rare Manifestation of Leptospirosis Pulmonary Miliary Condition P Thiry G Ablard and A Larcan[8] (Nancy) report an unusual case the second to be described in the world literature in which jaundice due to leptospirosis was associated with a pulmonary condition simulating miliary tuberculosis

Man aged 20 hospitalized with fever severe headache generalized muscular pain and intense headache had no gastrointestinal or pulmonary symptoms He had had no noteworthy illness during the preceding year Chest x rays revealed typical picture of miliary tuberculosis with scattered micronodular spots even in the apexes a left parahilar image suggesting lymphatic calcification Tuberculin skin tests produced a strong (3+) reaction Massive antituberculosis treatment with streptomycin para aminosalicylic acid and rimifon[*] begun at once proved ineffectual clinically and headaches increased Albuminuria of 0 60 was found on urinalysis and three days later jaundice appeared suggesting together with the renal syndrome diagnosis of leptospirosis which was confirmed by serologic studies Streptomycin therapy was continued for a fortnight and as both hepatonephritic condition and miliary signs regressed together it seems certain that leptospirosis was responsible for the unusual miliary picture

Though pulmonary manifestations of leptospirosis are often slight they may occasionally dominate the clinical picture and present serious diagnostic problems as in the present case in which all initial findings pointed to clearcut diagnosis of miliary tuberculosis

Tropical Eosinophilia Treated with ACTH K S Sanjivi K V Thiruvengadam and H C Friedmann[9] (Madras) believe that tropical eosinophilia is a manifestation of vascular allergy, the vessels of the pulmonary parenchyma being the basic shock tissue as compared with the bronchioles in asthma The remarkable increase in total white blood cells and in eosinophils to 50% or over indicates that hemopoietic tissues participate in the general allergic response Low grade fever cough with an asthmatic wheeze, anorexia and loss of weight are the main symptoms Physical examination reveals the signs of asthmatic bronchitis Chest x rays show various degrees of mottling with densities scattered diffusely through both lung fields

The authors treated 24 patients aged 12 56 with increas

(8) P se m d 63 729 730 M 14 1955
(9) D Ch t 28 76-87 J ly 19 5

ing intravenous doses of ACTH for 10 days The patients were discharged two or three days following termination of therapy and were followed for 6 12 months

Of the 24 patients 22 had satisfactory remission of symptoms and signs on the average by the third day of treatment Physical signs in the chest showed a corresponding or slightly delayed clearing All patients felt well After a marked drop in the eosinophil count there was a tendency to rise with tapering off of ACTH dosage and within a week of cessation of treatment the counts definitely rose usually to about half the initial values There was increased 17 ketosteroid excretion during midtreatment in most instances and the trend in values did not universally follow the change in clinical course The sedimentation rate fell gradually as a result of ACTH therapy corresponding to the reduction in eosinophils and in symptomatology In every patient there was appreciable improvement in x ray appearance of the lungs

It is felt that ACTH has a definite though limited place in treatment of tropical eosinophilia

THE BLOOD *and* BLOOD-FORMING ORGANS

WILLIAM B CASTLE MD

PART III

THE BLOOD AND BLOOD-FORMING ORGANS

GENERAL CONSIDERATIONS AND SPECIAL TECHNICS

In Vitro Studies of Erythropoiesis II Effect of Anoxia on Heme Synthesis was studied by E D Thomas[1] (Harvard Med School) who noted that though former workers had established the erythropoietic effect of anoxic anoxia of arterial blood others had failed to prove that low oxygen tension *in the bone marrow is the basis of the erythropoiesis* elicited by anemia of different origins Having previously shown that hemin synthesis by bone marrow in vitro does not necessarily parallel oxygen consumption Thomas determined the ability of rabbit bone marrow to synthesize hemin under various oxygen tensions in the Warburg apparatus in the presence of Ringer s phosphate and serum Gas mixtures of O concentration varying from 100% to complete anoxia were used and synthesis of hemin was expressed as per cent of radioactive hemin synthesized from glycine 2 C^{14} by *marrows exposed to air*

No definite effect of oxygen tension on hemin synthesis was noted until levels below 4% O were reached when synthesis diminished No appreciable synthesis was found in the complete absence of O

Thomas concludes that the failure to observe a stimulating effect from any level of reduced oxygen tension indicates that anoxia is not a direct stimulant of the bone marrow This is in conformity with the work of others using different methods and these facts may be considered indirect evidence *favoring a humoral regulator of bone marrow activity*

(1) Blood 10 61 615 J 1955

Erythropoietic Function in Dilution Anemia was investigated by *Allan J Erslev*[2] *(Fort Devens Mass)* who produced acute and pronounced dilution anemia in rabbits

METHOD —(1) Four rabbits were bled 20 ml /kg and the blood volume was immediately replaced by an equal volume of 6% dextran (2) Four rabbits received 25 ml /kg of 6% dextran intravenously every 12 hours for 4 days (3) Three rabbits were bled 20 ml /kg with prompt replacement of the blood by 6% dextran and then further administration of 25 ml /kg of 6% dextran every 12 hours for 4 days In every rabbit hemoglobin concentrations were determined spectrophotometrically each day on venous blood and daily reticulocyte counts were made in duplicate Tibial bone marrow examinations for per cent of normoblasts were made before the test situation and four days after

In rabbits bled with dextran replacement (1) there was a marked fall in hemoglobin a mean increase in marrow normoblasts from 28% to 49% of nucleated hemopoietic cells and a marked reticulocytosis (even when corrected to per cent of prebleeding red blood cell count) In rabbits given dextran only (2) a comparable drop in hemoglobin concentration was attained but no significant change in reticulocyte counts or marrow normoblasts occurred *In rabbits both bled and* further dextran diluted (3) results were closely similar to those in rabbits bled only showing that neither dextran nor hypervolemia interfered with erythropoietic activity

Interpretation of lack of compensatory erythropoiesis in dilution anemia due to hypervolemia requires consideration of the fact that cardiac output is increased in hypervolemia so that tissues can be supplied with normal amounts of oxygen without decrease in venous oxygen tension thus maintaining *capillary and tissue O tension near normal*

The author considers that the facts indicate that it is the tissue tension of O and not the O_2 content per unit of blood which regulates red cell production The tissue responsible for erythropoietic regulation is still unknown the work of others having failed to demonstrate a measurable fall in marrow O tension in anemia

• [Increased O transport to the tissues because of hypervolemia and increased cardiac output correlates well with the hemodynamic phenomena of pregnancy defined by Burwell Erslev s observations explain why the progressive physiologic anemia of pregnancy is not obliterated by an erythropoietic response —Ed]

(2) Blood 10 616 6 2 June 1955

Erythropoietic Action of Plasma Filtrate in Hypophysectomized Rats is described by Albert S Gordon Sam J Piliero Myron Tannenbaum and Charles D Siegel[3] (New York Univ) It has been demonstrated that erythropoietic effects produced in the intact rat by a filtrate obtained from boiled plasma of rabbits made severely anemic by phenylhydrazine were as pronounced as those evoked by anoxic stimuli In view of the suggestion that the extract might find application in treatment of refractory anemias in man its influence on the anemia of the hypophysectomized rat was tested

The boiled plasma filtrate evoked a significant erythropoietic response in hypophysectomized rats Red cell counts hemoglobin and hematocrit values were augmented approximately 15 20% reticulocytes displayed more than a 300% increase Striking changes were noted in the bone marrows of treated rats Whereas marrows of untreated long term hypophysectomized rats are usually pale and fatty those of the treated animals were grossly reddened due most likely to erythroid cell hyperplasia involving a doubling in percentages of nucleated erythrocytes within the femoral marrow Various peripheral white cell parameters examined were unaffected by the plasma filtrate Within bone marrows however significant decreases were observed in percentages of neutrophilic myeloid elements No other leukocytic values were altered by the experimental treatment

Anemia in the hypophysectomized animal has thus far been ameliorated only by endocrine replacement by lowered barometric pressures and by inorganic cobalt Iron copper folic acid vitamins B_1 B B_6 B_1 and C pantothenic acid liver extracts and protein hydrolysates given singly or in some combinations have exerted little or no effect

The authors results lend further support to the concept of a circulating erythropoietin in animals subjected to anoxia The site of formation and mechanism of action of this factor are now under investigation

• [Several studies reported in the literature concerning the erythropoietic factor may be divided into those finding erythropoietic effects only with unboiled plasma extracts and those which as here find similar effects with boiled extracts Erslev and Lavietes (Blood 9 1055 1061 November 1954) reported the erythropoietic factor to be nondialyzable and to

(3) P oc Soc E pe B l & M d 89 246-248 J 1955

be present in the serum of anemic rabbits and monkeys On the other hand Linman and Bethell (Blood 9 310 323 April 1956) using rats as test animals review and confirm the reports of others who have found erythropoietic activity in boiled plasma extracts A final conclusion remains to emerge from these apparent contradictions —Ed]

Splenic Function Study of Rationale and Results of Splenectomy in Blood Disorders is presented by F G J Hayhoe and Lionel Whitby[4] (Cambridge Univ) Physiologic activities of the spleen include reservoir function and sequestration of erythrocytes hemopoietic activity at certain phases of life phagocytic and reticuloendothelial activity possibly hormone production and capacity to elaborate antibodies Clinical disorders involving defects of splenic function commonly result from the sum of several effects and much less often from an isolated abnormality of a single splenic function *Splenectomy may be of value in treatment of certain well defined conditions*—hereditary spherocytosis (congenital hemolytic icterus or acholuric jaundice) idiopathic acquired hemolytic anemia and idiopathic thrombocytopenic purpura There are also various disorders associated with peripheral cytopenia often called hypersplenic syndromes either primary or secondary according to whether other demonstrable disease involving splenomegaly is present

Although splenectomy is uniformly successful in hereditary spherocytosis there is no primary disorder of splenic function The disease is thought to be due to a fundamental inherited defect in erythrocyte architecture and enzymatic constitution which leads to deformity and spherocytosis Spherocytes are selectively destroyed by normal splenic activity After splenectomy there is diminution in spherocytosis *paralleled by almost invariable decrease in osmotic fragility* which nevertheless continues outside the normal range

In autoimmune idiopathic acquired hemolytic anemia the spleen contributes partially to formation of autoantibodies and phagocytic reticuloendothelial activity may be increased but the disease may best be regarded as a primary disorder of the plasma protein and antibody forming mechanism Splenectomy is successful in improving the condition substantially or in producing clinical cure in about 50%

(4) Q J Med 24 365 391 October 1955

of cases Unfortunately neither clinical or laboratory features nor response to cortisone or corticotropin supply information indicating whether splenectomy is likely to succeed or fail [According to Jandl *et al* (Clin Res Proc 3 95 1955) detection of a high and progressive rate of autologous Cr^{51} labeled red cell sequestration by measurement of gamma radiation over the spleen suggests that splenectomy will be beneficial at least temporarily —Ed]

Idiopathic thrombocytopenic purpura previously thought due primarily to splenic hormonal or phagocytic overactivity must now be regarded at least in a substantial proportion of cases as immunoallergic Splenic contribution to autoantibody formation may not be important and success of splenectomy in many may be attributed chiefly to removal of a major thrombocytolytic site Splenectomy is not indicated in acute cases unless control by platelet rich blood transfusion and cortisone proves ineffective especially since operative risk in acute severe purpura is considerable but if the spleen is removed successfully duration of the disease may be curtailed In chronic idiopathic thrombocytopenic purpura splenectomy leads to complete remission in over 70% of cases and undoubtedly is the treatment of choice

Many combined or isolated cytopenias with active bone marrow and splenomegaly usually regarded as examples of primary or secondary hypersplenism may in fact be further immunoallergic disorders with a primary abnormality involving the antibody producing system Nevertheless splenectomy is often successful in such cases whether by removal of a site of antibody formation by reduction in cytolysis or by removal of an organ producing an excess of marrow regulating hormone Primary hypoplastic pancytopenias without splenomegaly do not improve after splenectomy but operation might be justified if palpable splenomegaly or a moderately active marrow were encountered in an otherwise typical aplastic anemia In leukemia and myelosclerosis when transfusion requirements are large splenectomy may produce great improvement in the anemic state especially if evidence of hemolysis is found

Heinz Bodies in Red Cells after Splenectomy and after Phenacetin Administration A review by Webster (1949) of

early theories on the mechanism of Heinz body formation is cited by J G Selwyn (Postgrad Med School London) The generally accepted view is that Heinz bodies are particles of denatured hemoglobin formed generally in mature red cells (occasionally in reticulocytes) in the course of an irreversible reaction with a toxic substance The presence in

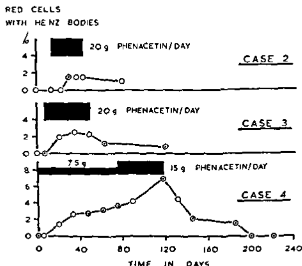


Fig 57 — Development of Heinz bodies in red cells of three patients after administration of phenacetin Case 4 was probably splenic atrophy (Courtesy of Selwyn J G Brit. J Haemat 1 173 183 April 1955)

vivo of large numbers of Heinz bodies is usually associated with hemolytic anemia Whether Heinz body formation per se causes destruction of affected red cells and what part the spleen plays in this destruction are not known The spleen apparently can either filter off affected red cells from the circulation or somehow remove Heinz bodies from red cells

Selwyn reports small numbers (0 1 3%) of Heinz bodies in red cells of 17 of 31 patients studied 30 of whom had had splenectomy and 1 had probable splenic atrophy Four with Heinz bodies were known to have taken phenacetin recently Sepsis may have been a factor in two other patients Of the remaining 11 6 were not in good health but no reason for Heinz body formation could be found

(5) Brit J Haemat 1 173 183 April 1955

Woman 58 had small numbers of Heinz bodies consistently present in the blood and large numbers appeared during administration of tablets containing 4 gr each of aspirin and phenacetin and 1/8 gr codeine phosphate On separate occasions when intestinal activity was disturbed by a leaking jejunostomy and by large bowel obstruction Heinz bodies became even more numerous Normal red cells given by transfusion developed large numbers of Heinz bodies and survived for a maximum of about 80 days

Phenacetin tablets (5 gr) were administered to two other patients who had undergone splenectomy and tablets containing 3½ gr aspirin 2½ gr phenacetin and ½ gr caffeine were given to another patient with probable splenic atrophy In all three small numbers of Heinz bodies appeared in the red cells after administration of the drugs for two to three weeks (Fig 57)

Absence of the spleen or of splenic function is apparently essential for the appearance of Heinz bodies after taking phenacetin in normal doses Heinz bodies were never found in the blood of many nonsplenectomized patients who were taking the drug

Erythrocyte Preservation Topic in Molecular Biochemistry is discussed by Beverly W Gabrio Clement A Finch and Frank M Huennekens[6] (Univ of Washington) When whole blood is withdrawn from the donor and stored at 4 C in standard acid citrate dextrose (ACD) medium plasma is quite stable for extended periods However erythrocytes begin to deteriorate within a few days exhibiting decreased ability to metabolize glucose loss of K from within the cells and replacement by Na increased osmotic and mechanical fragility and decreased ability to survive when transfused Maximum storage permissible is 21 days when approximately 70% of ACD stored cells will survive after transfusion

The principal approaches to erythrocyte preservation are (1) to arrest metabolic activity by storing cells at subzero temperatures in glycerol and (2) to control metabolism of cells at 4 C by addition of metabolic substrates or inhibitors In studies directed toward the latter approach the authors established initially that erythrocyte deterioration was not due to extraerythrocytic factors such as composition of the preservative ACD fresh aged or dialyzed plasma leuko

(6) Blood 11 103 113 Feb y 1956

cytes reticulocytes *platelets* or *hemolysates (with and with out stroma)* and the *gas phase* (O_2 *N_2 or air*) *From these* results and the fact that ability to withstand storage was un related to in vivo age of cells i e 0 120 days deterioration was attributed to some internal metabolic failure Since de terioration and loss of membrane integrity imply a con comitant loss of energy potential the qualitative and quan titative pictures of phosphate containing compounds in the erythrocyte were examined particularly ATP (adenosine triphosphate) A general parallelism was found between decline in certain high energy phosphate compounds and a decline in physiologic viability of the cells By tagging *indi vidual cell populations with* separate iron isotopes (Fe^{55} *and* Fe^{59}) *it* was shown *that deteriorated cells could be restored to normal* when *transfused* back *into active circulation*

This led to a *search* for a *relevant chemical* substance that could *duplicate the restorative action of more complex sys tems* ATP or other phosphate esters cannot be added as phosphorylated substances do not readily penetrate the erythrocyte membrane However when nonphosphorylated substances related to ATP were added to stored cells the nucleoside adenosine served as an excellent rejuvenant When cells stored for 28 days were incubated at 37 C for one hour with adenosine there was rapid and noticeable return of the *intracellular phosphate pattern* to *its normal state* Adenosine *is effective in rejuvenating* cells already *deterio rated* and *when added to fresh cells in prolonging the stor* age period to 40 50 days To achieve the maximal effect about 2 500 μM adenosine (of which about 60% is absorbed) had to be added for each 100 ml red cells Cells so rejuve nated must be washed by centrifugation to remove unab sorbed nucleoside which produces transient hypotension on intravenous administration

Various purine (but not pyrimidine) nucleosides such as inosine adenosine guanosine xanthosine and *deoxyadeno* sine were *effective in restoration of stored cells Effective* ness of *adenosine during storage seems* best explained by the *assumption* that it is converted first to inosine and split sub *sequently* by the phosphorylase since an adenosine deami nase has been demonstrated in the erythrocyte and in resto

ration experiments with adenosine an accumulation of both inosine and hypoxanthine but not adenine has been observed Consequently it is believed that inosine rather than adenosine is the nucleoside of choice for preservation of blood Erythrocytes can be stored equally well with either but inosine does not exhibit the toxic properties shown by adenosine on intravenous administration Inosine is the actual substrate for the phosphorylase reaction use of adenosine introduces an additional substance ammonia into the system

Much remains to be done on erythrocyte metabolism but some physiologic functions of the erythrocyte and their control by underlying enzyme systems are beginning to be understood

• [This is an excellent example of the value of a systematic approach along theoretical lines to a practical problem The arti le should be read in it entirety —Ed]

Mechanics of L E Cell Phenomenon Studied with Simplified Test are presented by I Snapper and Daniel J Nathan[7] (Brooklyn)

TECHNIC —Substrates of normal polymorphonuclear cells are prepared by placing a rubber ring (section of rubber tubing with internal diameter of 0 5 cm and height of 0 2 cm) on the center of a clean glass slide The area of the slide enclosed by the ring is filled with 1 or 2 drops of finger or venous blood from a nonlupus patient and the slide is gently placed in a Petri dish the bottom of which has been covered by moist filter paper The covered Petri dish is incubated at 37 C for one hour The slide is removed held perpendicular to the table top while the rubber ring is gently slid away and dried in this position The area which had been encircled by the ring contains large numbers of sedimented white cells with a variable coating of red cells These preparations may be washed with saline or serum Many rings can be prepared whenever venous blood has to be drawn for other tests Substrates can also be made from relatively thick smears of blood from leukemia patients or from dried imprints of various carcinomas and Hodgkin s tissue

A drop of blood from a finger or ear of a suspected lupus patient is affixed by gently touching the center of a clean cover glass (24 × 50 mm) The hanging drop of lupus blood is allowed to come in contact with the ring of normal white cells or the leukemia smear by resting the end of the long cover glass on broken pieces of cover glass previously laid on the substrate slide The preparation is placed in a moist Petri dish and incubated one to two hours The slide is removed and the cover slip gently lifted from its supports If the clot is not removed

(7) Blood 10 718 7 9 J ly 1955

with the cover glass it is dislodged carefully with a sharp splinter of cover glass Excess serum is quickly removed by forceful tapping The preparation is dried quickly and stained by the Wright or (after fixation in methanol) Giemsa methods Area beneath the clot is examined for L E cells

In case only serum of L E suspect is available 2 drops of normal fresh blood are mixed with an equal amount of suspect serum in a small Widal tube After coagulation the clot is decanted onto a clean filter paper to remove excess serum and then positioned over the substrate slide as in the hanging drop technic

Both ring substrates and leukemia smears proved effective several weeks after preparation but they appeared to give best yield of L E cells when not over a week old

No false positive results were obtained in 30 healthy persons or 50 patients with various diseases Striking results in demonstration of L E cells by this method were obtained in 20 of 21 known cases of disseminated lupus erythematosus In several instances over 100 L E cells could be seen in a low power field The one case that yielded no lupus cells by this method yielded only a solitary L E cell by the Lee method

In the present preparations L E cells that possess all characteristics of the Hargraves cell are always present However in other cells the inclusion instead of taking basic stains is often faintly to strongly eosinophilic The inclusion in these cells often appears somewhat foamy and is totally divested of any nuclear structure and multiple included masses (droplet cells) are frequently seen With the staining methods used these inclusions like those of classic Hargraves cells apparently represent masses of markedly depolymerized desoxyribose nucleic acid Since dried cancer cells and Hodgkin s tissue imprints can also be used as substrates it appears that desoxyribose nucleic acid of the nuclei of many different cells can be depolymerized by the lupus factor and become material from which lupus cell inclusions are formed For formation of L E cells it seems necessary that living polynuclear leukocytes dead cells and lupus serum be brought together Lupus serum can depolymerize desoxyribose nucleic acid of nuclei of dead but not of living cells Depolymerized material is then phagocytized by living polynuclear cells and formation of lupus cells results

Some Factors Influencing Formation of L E Cells Method for Enhancing L E Cell Production devised by William H Zinkham and C Lockard Conley[8] agitates and traumatizes leukocytes before preparation of buffy coat smears

Technic—Fresh venous blood 5 ml is placed in a dry test tube containing 1 mg sodium heparin Within two hours 1 5 ml is transferred to a 50 ml Erlenmeyer flask containing 15 glass beads 4 mm in diameter The flask is placed in a rotating device similar to that for determining mechanical fragility of red cells The flask is rotated at 40 rpm for 30 minutes at 37 C After rotation 1 ml blood is transferred to a Wintrobe hematocrit tube and centrifuged at 1 000 rpm for 10 minutes The buffy coat layer is then pipeted off smeared on cover slips and stained with Wright s stain

When this rotation technic was applied to blood from 132 patients with diseases other than systemic lupus erythematosus no L E cells or extracellular material was found Blood from 16 patients which showed L E cells by standard technics revealed a striking increase in L E cells and extracellular material after rotation in most instances Blood from 11 of these studied by both rotation and clotted blood technics showed more L E cells in the rotated specimens in most instances although in 3 the clotted blood technic produced more L E cells Blood from 10 patients with clinical evidence of lupus erythematosus which had been repeatedly negative with L E cell tests continued to give negative results with the rotation and clotted blood technics

A generally accepted theory of L E cell formation is that L E plasma factor induces a specific chemical change in leukocytic nuclei possibly depolymerization of desoxyribose nucleic acid Altered nuclei are later ingested by other leukocytes to form L E cells This concept explains the distinctly altered appearance and staining characteristics of inclusion bodies and also extracellular material and rosettes The assumption that L E plasma factor is unable to attack intact living cells explains the absence of L E cells from the circulation Presumably leukocytes are removed at end of their life span in such a way as to preclude participation in formation of L E cells In a test tube however dying leukocytes are readily available as nuclear material for L E transformation These experiments support this hypothesis

Extracellular material so regularly found in positive L E

(8) B ll J h H pk Hosp 98 10 118 F bru ry 1956.

cell preparations is of particular interest This amorphous hyaline globular substance, identical in staining characteristics with L E cell inclusion bodies, is lysed by desoxyribonuclease It seems likely that formation of this material probably from nuclei of injured or dead leukocytes under the influence of L E plasma factor is the primary stage in L E cell formation

Acute Cardiac Tamponade Complication of Sternal Marrow Aspiration successfully diagnosed ante mortem and treated has never before been reported according to Louie B Jenkins Bernard E Ferrara and Hollis P Snead[9] (Charleston S C)

Man 24 with severe progressive cardiovascular renal disease azotemia anemia blood pressure of 212/124 and venous pressure of 19? mm saline was subjected to sternal marrow aspiration in the mid ternal line at the level of the second interspace The specimen was reported to be peripheral blood and a second aspiration was made with a 16 gauge, 1¼ in needle introduced 1 cm below the previous site The operator advanced the needle more deeply than usual to avoid peripheral blood The patient felt weak and nauseated and one hour later vomited and noted sternal pain worse on breathing Blood pressure was 80/60 pulse rate 65 Breath sounds were depressed over the right anterior thorax but an ECG and chest x ray showed no change Six hours later with continued hypotension heart sounds were decreased and fluoroscopy showed decreased cardiac pulsations Pericardiocentesis yielded 175 cc of dark blood Blood pressure rose only to fall again in two hours, and venous pressure was 200 mm A repeat tap yielded 40 cc of dark blood The next day a pericardial friction rub was noted and venous pressure was 160 mm Bleeding clotting and prothrombin times were normal Despite recovery from this episode the hypertensive renal disease progressed and the patient died one month after hospitalization There was no autopsy

In the 13 fatal cases described in the literature (10 with autopsy) the symptoms were similar with signs of circulatory failure then cerebral hypoxia and death following in 10 30 minutes Hemopericardium arose from laceration of the right ventricle in most of the cases others showing laceration of the myocardium pericardial tear and laceration of the ascending aorta In some the sternum was the site of pathologic processes such as neoplasms Difficulty in obtaining marrow was usually reported

The authors emphasize the dangers of deep sternal pene

(9) A M A Arch S g 71 89 895 December 1955

tration and the desirability of less hazardous sites of marrow aspiration They suggest that a patient showing circulatory failure after sternal puncture should have immediate pericardiocentesis

Thyroid Function Studies on Children Receiving Cobalt Therapy were made by Charles H Jaimet and Henry G Thode[1] (Hamilton Ont) in further investigation of the antithyroid effect ascribed to cobalt by Kriss and his co workers Administration of a cobalt iron preparation providing 1 2 4 and 6 mg cobaltous chloride/kg body weight daily for 10 weeks caused no significant change in thyroid function in 17 children a measured by radioactive iodine uptake conversion ratio and saliva protein bound iodine activity ratio determinations No thyroid enlargement or clinical hypothyroidism developed in any patient

Results indicate that cobalt used in amounts up to 6 mg / kg / day for 10 weeks doe not affect any phase of thyroid function and has no goitrogenic action Thus even at dosage levels twice as great as Kriss and his associates used their findings could not be confirmed Several explanations appear possible None of the present patient had sickle cell anemia whereas in the other study conclusions concerning hypothyroidism were drawn solely from children with this disease However other studies with cobalt in patients with sickle cell anemia have al o failed to confirm these results Since cobaltous chloride is not an official drug specifications for medicinal quality are not available and possibly variations in the quality of the drug could be responsible for the findings of Kriss *et al* Toxic impurities in samples of commercially available cobaltous chloride have been reported

Since cobalt in vitro in cell free homogenates has been shown to inhibit tyrosine iodinase complete lack of its antithyroid effect in the present study suggests that it does not permeate the cells of the thyroid gland in vivo sufficiently to affect gland function These results of course do not preclude the possibility of a rare idiosyncrasy or of some disease that would raise the cells of the thyroid to a state permeable to cobalt

(1) J A M A 158 1353 1355 Aug 13 1955

Current Status of Hemolytic Disease of Newborn Victor C Vaughan III[2] (Temple Univ) notes that hemolytic dis ease due to A or B incompatibility is more common than that due to Rh factors (table) usually producing icterus in the first 36 hours of life The serum of the mother of such an

GENERAL FEATURES OF HEMOLYTIC DISEASE OF THE NEWBORN

	NO COM TIB LIT	TB LITY	THER
F equ cy f ancomp b l y be ween mother d infan	A 18% B ?% } 2 %	Rh, 8%	K ll, Kidd, S, et Variabl
F q ncy f hem lytic disease an l l incomp b l ty	3% f all ewb rn inf ts, invol ing bou 5% f an mpa bl m g	0.5% f all wborn inf ts, in lving bo 5% f incomp bl ma gs	V ry are
Seve ty f illness Stillb rth Kernicterus Sever h mol ic p ocess Mild icterus (icterus ly)	Usuall mild V ry rare Not rare Uncommon Common	Mild to sever Comm Comm in un ed Commo Not common	V riabl
A bod in the sy em N ural" Immun	 Yes Yes	 N Yes	 N Yes
Demonst on f coa ed cell in infan By Coombs est By colloid l m di	 Usually U ll	 U all U all	 U lly Often ot (K ll Duff)

By Rh ncomp t b l ty s m a t ncompat bil ty w th espect to th a t ge Rh D Other nt gen n the Rh ystem are o ly ely pons bl f h molyt d sease

affected infant usually contains antibodies against A or B cells that are different from the antibodies that most persons normally have in their particular blood group The latter A or B antibody active in physiologic saline (saline active antibody) is readily neutralized by A or B specific poly saccharide substances The mothers of affected infants however have other antibodies not active in saline (saline inactive antibodies) but demonstrable even after neutrali zation if cells and neutralized serum are combined in adult serum or other colloidal mediums Similarly in mothers sen sitized to Rh positive cells saline active antibodies may be demon rable but probably do not contribute to illness in

( ) Postgrad Med 18 115 12 A gu t 1955

the fetus This is probably due to saline inactive antibodies since they cross the placenta whereas the Rh positive cells do not except in small amounts in the case of saline active anti A or B antibodies

In the A and B and Rh systems the illness in the incompatible infant seems associated with saline inactive antibodies The presence of these correlates closely with the occurrence of hemolysins against A and B cells although cells coated with saline inactive antibodies against A and B cells do not give a clearly positive Coombs test reaction in most affected infants However spontaneous agglutination of antibody coated cells commonly occurs in protein solutions (or in 16% LePage s Strength Glue in physiologic saline solution)

Neonatal hemolytic disease may be classified in order of severity of disease as infants who are (1) stillborn with or without hydrops fetalis (2) live births succumbing to severe hemolytic disease (3) with kernicterus (4) able to recover completely from variably severe hemolysis and (5) Rh positive (or other incompatibility) but without clinical disease whose mothers have Rh (or other) antibodies against the infant s cells (table) Kernicterus is the only serious threat to life in infants born in reasonably good condition and should be entirely preventable

Anemia in hemolytic disease may be severe and rapidly progressive but progresses in an orderly manner and probably not with sudden hemolytic crises The fall in hemoglobin level may be delayed a day or more by continued compensatory activity in bone marrow and is not a reliable index of need for therapy Although individuals differ widely in susceptibility kernicterus becomes common at bilirubin levels over 30 mg/100 ml but is uncommon below 18 20 mg Whether or not bilirubin is at fault the disease seems controllable by exchange transfusion It should be assumed that jaundice in the first 24 hours of life is evidence of hemolytic disease due to blood group incompatibility

It seems safe to make a single determination for antibodies at or just after the thirty fourth week of pregnancy in the first as well as in subsequent pregnancies in Rh negative women with no history of previously affected children and

no blood transfusions In Rh hemolytic disease severest ill ness occurs when mothers have high titers of anti Rh substance or when severe disease occurred in previous sibling although prognosis cannot be absolutely reliable either for occurrence or severity of disease

Premature delivery even of two weeks greatly increases the incidence of kernicterus which is possibly related to the infant s capacity to excrete bilirubin Thus the criteria for early delivery are (1) no or only one living child (2) history of previous severely affected infants and (3) a homozygous husband Cortisone and ACTH during pregnancy probably are not helpful Affected infants tolerate anesthetic agents poorly so mothers should have local or regional anesthesia Severely affected infants often have cardiac failure so the cord should be clamped immediately after delivery rather than waiting until pulsation stops

Exchange transfusions are performed when the infant is *Rh positive (since blocking substances on cells may give a* false Rh negative test a positive Coombs test result should lead to further tests) and previous siblings had hemolytic disease requiring treatment if the maternal titer of anti Rh during pregnancy reaches 1 16 if delivery is premature in a sensitized mother or the infant with hemolysis has an en larged liver or spleen edema or pallor Jaundice is not a relia ble indication as even severely affected infants may appear anicteric at birth Simple transfusion is indicated when cord hemoglobin is under 15 Gm /100 ml or bilirubin over 3 5 *mg /100 ml Exchange may be required if serum bilirubin* rises to 15 mg in the first 24 hours or over 20 mg thereafter Multiple exchange may be necessary to stabilize bilirubin between 20 25 mg Transfusions should be with the freshest possible blood compatible with the mother s serum and checked by the indirect Coombs technic When this requires that O Rh negative blood be used in an infant with A or B blood type donor blood must not contain anti A or B ag glutinins of the immune (saline inactive) variety because these agglutinins are resistant to in vitro neutralization by A and *B blood group specific substances* However saline active antibodies can be neutralized by adding A and B blood group-specific substances

Acute Hemolytic Anemia Cryoglobulinemia and Cold Agglutination are reported in a case by Harold O Conn[3] (Yale Univ)

Woman 81 mildly diabetic had low back and jaw pain weakness fatigue and anorexia She took nitroglycerin and digitalis for mild cardiac failure Before hospitalization she noted dark urine She was semistuporous and icteric Examination revealed coarse rales at the lung bases cardiomegaly with grade 2 systolic murmur large liver and spleen and no other important findings Red blood cell count was 1 180 000/cu mm with hemoglobin of 4 7 Gm /100 ml hematocrit of 24% and reticulocytes 15% Sedimentation rate (Wintrobe corrected) was 65 mm /hour White blood cells were 10 000/cu mm with 83% neutrophils 9% lymphocytes and 8% monocytes Blood showed marked rouleau formation and microcytic hypochromic and sphero cytic cells Bone marrow howed marked erythroid hyperplasia Bilirubin level was 0 41 mg (direct) and 2 56 mg /100 ml (total) Autoagglutination even on warmed slide prevented typing Results of the Coombs test were strongly positive at room temperature but nega tive at 37 C Cold agglutinins (temperature not stated) were positive in 1 1 024 dilution but negative at 37 C Red cell fragility was normal

Cortisone administration led to marked clinical improvement over 10 days Cold agglutinins reached 1 1 048 576 titer Cryoglobulins which formed a gel on cooling below 10 C and dissolved on repeated warming measured 170 mg /100 ml Serum albumin level was 3 45 Gm and globulin 2 27 Gm /100 ml Paper electrophoresis showed only some lowering of albumin level Separated washed cryoglobulin electrophoresed at 37 C had a mobility of gamma globulin Although the hemoglobin level returned to 9 5 Gm /100 ml she died at home three months later from upper respiratory infection with evere jaun dice Autopsy was not performed

Although in the decade since the first report of cryoglobu linemia many cases have been studied this is the first re corded association with a very high titer of cold agglutinins With cryoglobulinemia about half the cases are eventually diagnosed as myeloma and a fifth as chronic lymphatic leu kemia Bone marrow studies here were not suggestive of such entities Stats and others have ascribed the hemolytic anemia that occasionally follows the development of very high titers of cold agglutinins to the increased mechanical fragility often found in cooled blood in vitro and presumably according to Ham in vivo in peripheral portions of the body

Biomicroscopic Observations on Conjunctival Circulation in Chronic Cryoagglutininemia with High Titers and in States Causing Sludged Blood are reported by A Marmont

(3) N w E gl d J Med 253 1011 1013 Dec 8 1955

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not true autoagglutination since all immunologic tests remained completely negative although addition of Hayem s solution to oxalated blood provoked flocculation of seroproteins seen microscopically as a granular precipitate with liberation of previously conglutinated cells

In 50 children with Bouillaud s disease degree of sludge



F g 58 (l ft) —Typ l h m g pp ra j l blood fl w n beta pla mocyt ma wh h p ted th gh m on f toagg g t on n t be dlik app f m ll l

F g 59 (ght) —S m la se w th toagg eg t on

(Cou t y f M mont A t / S hw m d W h sch 85 90 905 S pt. 20 1955)

followed approximately the clinical severity of rheumatic disease There was a general parallelism between agglomeration of erythrocytes in vivo and sedimentation rate i e in all cases with Katz index over 10 there was some aggregation *in vitro* *Nevertheless in some cases results of the two meth*ods did not agree as has also been reported by others Intravascular aggregation seems a more reliable and sensitive index of activity of the rheumatic process

Definite distinction must be made between phenomena of

F de Matteis and L Mariotti[4] (Genoa) in 4 patients with acquired autoimmunologic hemolytic anemia 39 patients *with marked disturbances of blood proteins due to* various causes and 50 infants with acute articular rheumatism (Bouillaud)

Among those with immunohemolytic anemias two patients with incomplete cold antibodies presented no significant changes either in circulating blood or in stability of blood suspensions in vitro Biomicroscopic studies were made while direct Coombs test gave positive reactions but remission of hemolysis had been obtained with cortisone

The most striking circulatory changes were observed in chronic cryo agglutininemia particularly in a case of chronic benign lymphadenosis in which the level of cold agglutinins was extremely high (1 65 536 in saline solution) After brief refrigeration (perfusing the bulb with cooled physiologic serum or placing a small piece of ice in contact with the closed lid) the blood stream previously perfectly homogeneous and agranular suddenly appeared fragmented A true circulatory segmentation occurred since on prolonging the examination as the cold effect was diminished cylindric erythrocytic agglutinations obstructing each small vessel with adhesive casts were gradually displaced en bloc leaving between them clear plasma lacunas The entire reaction generally lasted 20 30 seconds

In adults with various diseases all degrees of intravascular agglomeration were observed with marked changes in hepatic cirrhosis malignant lymphogranulomatosis amyloidosis pleurisy etc In all cases there were comparable changes in stability of blood suspension in vitro with marked elevation of sedimentation rate (100 mm or more in 1 hour) strongly positive reactions of serum colloidal lability and noticeable disturbance in electrophoretic composition Sludged blood was encountered at its maximum in two cases of beta plasmocytoma in which the blood became inhomogeneous and fragmented with definite demarcation between so-called basic masses and plasma lacunas (Figs 58 and 59) In these same cases there was evident agglomeration even macroscopically of oxalated or citrated fresh blood it was

(4) Schw m d Wchnschr 85 90 905 S pt 0 1955

centrifugation examined for hemolysis Erythrophagocytosis in white cells is demonstrated by routine blood smears

In three cases of acquired hemolytic anemia with warm autoantibodies immersion for 30 minutes at 40 C caused erythrophagocytosis but no hemolysis In three cases of acquired hemolytic anemia with cold agglutinins exposure for 30 minutes at 20 C produced hemolysis and some erythrophagocytosis the latter was better demonstrated by further immersion at 40 C In paroxysmal cold hemoglobinuria hemolysis and phagocytosis were demonstrated after 10 minutes exposure at 5 C followed by 10 minutes immersion at 40 C In two cases of paroxysmal nocturnal hemoglobinuria (Marchiafava anemia) strong hemolysis was produced by 30 minutes immersion at 40 C but erythrophagocytosis was questionable Negative results were obtained in hereditary spherocytosis hereditary nonspherocytic hemolytic disease thalassemia major and pernicious anemia

The authors suggest that this test should be used in routine diagnosis of hemolytic disease In general results are expected to be positive in diseases conditioned by blood antibodies In chronic idiopathic acquired hemolytic anemia with incomplete warm autoantibodies for example in which clinical remission followed cortisone treatment direct antiglobulin test reactions were still positive but phagocytosis tests were negative Whether the test will be positive in other hemolytic anemias awaits systematic investigation In sickle cell anemia erythrophagocytes have been reported in the peripheral blood and analogous observations have been made in toxic hemolytic states and in certain infectious diseases and in these positive results are expected

• [Ehrlich s introduction of stains for blood cells was an advance of vast importance but it led to neglect of microscopic study of fresh blood which in the hemolytic anemias may be especially revealing and useful In this article a simple technic of in vivo chilling (or incubation) of blood in digital vessels extends another of the master s experiments in pathologic physiology to a wider group of hemolytic anemias —Ed]

Acquired Hemolytic Anemia and Viremia was investigated by Herbert R Morgan[6] (Univ of Rochester) in eight patients—two with chronic lymphocytic leukemia six with no other associated disease In three splenic tissue and blood were tested in one splenic tissue only and in the other four

(6) J Lab & Cl M d 46 580 58 O t b 1955

agglutination and of erythrocytic aggregation In both an autoagglomeration of red blood cells is involved influenced by serum protein factors but whereas true agglutination is the expression of an immunologic phenomenon aggregation is merely a biophysical reaction Electron microscopy has shown that the Knisely substance forms as an amorphous coating covering the entire erythrocyte surface and that antierythrocytic antibodies (agglutinins of systems ABO incomplete Rh antibodies and autoantibodies) are recognizable as fine filaments of plasma (not extrusions from cells) thrust under extremely small elevations of the blood cell surface These differences are reflected in profound physiopathologic and clinical differences True autoagglutinations are almost invariably associated with hyperhemolysis which is lacking in most conditions characterized by sludged blood Thus at the most Knisely substances play the doubtful role of *simple opsonins* but certainly *not of immune erythrotropins* seen in human hemolytic anemias Coated cells of sludged blood are neither filtered nor sequestered by the spleen they are not phagocytized or lysed i e they are not damaged by true antibodies Furthermore circulatory changes in small vessels (cyanosis Raynaud s phenomena etc) are never seen with sludged blood but these are common in cryoagglutininemic states

• [It is never entirely clear how much sludging of the blood as a result of the action of cold is the result of diminished local blood flow from vasospasm with consequent rouleau formation The observation that in patients with rapid sedimentation rates pressure on the eyeball sometimes at once causes segmentation of the column of blood in the vessels of the retina is a case in point —Ed]

Use of Ehrlich s Finger Test for Demonstration of in Vivo Hemolysis and Erythrophagocytosis in Hemolytic Diseases is described by H Schubothe and W Muller[5] (Univ of Freiburg) In 1881 Paul Ehrlich described a test in which a finger was *cooled then warmed with subsequent* withdrawal of capillary blood to demonstrate intravascular hemolysis in syphilitic paroxysmal cold hemoglobinuria

TECHNIC —A tourniquet is placed around a finger which is then immersed for 10 30 minutes in a water bath at 5 20 and 40 C Time and combinations of temperatures are varied according to type of case Blood from the finger is collected into capillary tubes and after

(5) Klin Wchschr 33 27 276 Mar 15 1955

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(5) Kl W h schr 33 27 6 M 15 1955

24 hours causes pronounced increase in osmotic and mechanical fragility surpassing significantly that seen in normal blood

Pathologic significance of the erythrocytic defect in hereditary spherocytosis has not been explained Neither toxic processes nor immune mechanisms have been established in typical cases The Coombs test and tests for hemolysis with acidified serum and complement give negative results Splenectomy in hereditary spherocytosis is almost invariably followed by rapid alleviation or elimination of anemia and jaundice with simultaneous decrease in excretion of bile pigment and in number of circulating reticulocytes indicating that the effect of this procedure is to decrease blood destruction rather than to increase blood production Regardless of their improved status patients retain their cell defect following splenectomy

Charles P Emerson Jr Shu Chu Shen Thomas Hale Ham Eleanor M Fleming and William B Castle[7] (Harvard Med School) studied 31 patients with hereditary spherocytosis 13 of them before during and after splenectomy Three were examined after splenectomy performed 4 20 years earlier in 15 spleens had not been removed Observations were made to determine whether cells with a pronounced abnormality are found in the spleen and if so whether this results from normal or abnormal activity by the spleen Comparisons were made between blood from the splenic vein and from splenic pulp

The spleen in hereditary spherocytosis functions normally in relation to normal erythrocytes as indicated by the normal life span of normal donor cells Moreover donor (unagglutinable) cells present in spleens of patients who have had recent transfusions exhibit little or no increase in osmotic fragility in contrast with marked abnormality of the patients cells predominating in that organ

In patients whose spleens were removed continuous production of abnormal red cells is a constant and permanent feature of hereditary spherocytosis The defect which persists despite cure of anemia is manifested by abnormally increased osmotic and mechanical fragilities of red cells which

(7) A M A A b I t Med 97 1 38 J y 1956

blood only Others have reported the isolation of viruses from the blood of patients with acquired hemolytic anemia

METHOD —Specimens of whole clotted blood or spleen were frozen and stored at —40 C later thawed ground with alundum and suspended in beef heart infusion broth to which 100 units of penicillin and streptomycin/ml was added The suspensions were injected as follows 0 1 ml into the amniotic sac of 10 day old chick embryos 0 2 ml into the allantoic sac of 8 day old embryos and 0 5 ml into the yolk sac of 7 day old embryos The eggs were incubated at 35 C and examined daily for four days when the fluids were harvested and tested with 0 5% suspension of chicken erythrocytes for presence of hemagglutinating viruses *Three serial blind passages* were carried out on each specimen with testing for hemagglutinating agents on fluids from each passage The fluids and a suspension of yolk sac tissues from the third blind passage were inoculated on chorioallantoic membranes of 11 day old chick embryos incubated five days at 35 C and the membranes were then examined for lesions

Absence of death of embryos presence of visible changes in embryos hemagglutination tests on egg fluids and absence of development of lesions on chorioallantoic membranes demonstrated that it is unlikely that such viruses as Newcastle disease influenza mumps psittacosis, herpes certain pox viruses and closely related agents occurred in the blood or splenic tissues of patients and that viremia due to these viruses is not common in patients with acquired hemolytic anemia

Studies on Destruction of Red Blood Cells IX Quantitative Methods for Determining Osmotic and Mechanical Fragility of Red Cells in Peripheral Blood and Splenic Pulp Mechanism of Increased Hemolysis in Hereditary Spherocytosis (Congenital Hemolytic Jaundice) as Related to Functions of Spleen Hereditary spherocytosis is an inherited disease characterized by chronic anemia increased hemolysis and erythropoiesis and frequently splenomegaly Its classic feature is presence in peripheral blood of spheroidal red cells unusually susceptible to hemolysis when suspended in hypotonic mediums Increased osmotic fragility reflects that the surface membrane of the erythrocyte is reduced in size relative to volume so reducing the capacity to swell before reaching the spherical configuration These cells in plasma are also abnormally susceptible to trauma thus exhibiting increased mechanical fragility Incubation at 37 5 C for

There is direct evidence in vivo that the spleen in hereditary spherocytosis sequesters the individual's own red cells. The mechanism for this selective removal is not established but may be related to the abnormal spheroidal shape of the red cells. The spleen seems to condition red cells which it sequesters as evidenced by alteration of osmotic and mechanical fragilities. Figure 60 shows the osmotic fragility of red cells in different samples from spleen compared with those in peripheral blood before and after splenectomy. Comparative curves show progressive increase in proportion of abnormal cells in samples from the peripheral vein, splenic vein, splenic pedicle and splenic pulp, respectively. Osmotic fragility of spleen samples exceeded that of any sample from peripheral blood before or after splenectomy. Although the mechanism for final destruction of red cells is not known, it is probably related to increase in osmotic and mechanical fragilities.

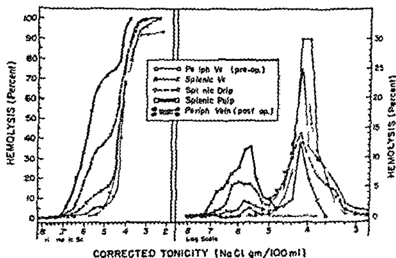
It is inferred from these observations that the function of the spleen in hereditary spherocytosis may be normal and that the inherited defect is limited to the red cells. Thus it may be presumed that normal functions of the spleen include selective sequestration of spheroidal red cells from the general circulation and conditioning of such cells so that they are incapable of prolonged survival.

Abnormalities of Carbohydrate Metabolism of Red Cells in Hereditary Spherocytosis (HS) are reported by Thomas A. J. Prankerd, Kurt I. Altmann and Lawrence E. Young[8] (Rochester, N. Y.). The rate of incorporation of P^{3} labeled orthophosphate into phosphate esters of red cells was measured by extraction of phosphates at intervals from red cell stroma and from remaining intracellular material and measurement of radioactivity in chromatographically isolated compounds. Of the 18 patients studied, 13 were studied before and after splenectomy.

In the normal erythrocyte, 2,3 diphosphoglycerate (2,3 DPG) constantly has a higher relative specific activity than adenosine triphosphate (ATP), compatible with the hypothesis that the former compound is a precursor of the latter. In all HS patients studied, the intracellular P^{32} phosphate

(8) J. Cl I t 34 1 68 1275 A g t 1955

become abnormally increased by incubation at 37 5 C Before splenectomy distribution curves of osmotic fragility instead of being monophasic and symmetrical are asymmetrical and biphasic in most cases due to the absence apparently by removal of a large proportion of cells showing hemolysis at tonicity levels above 0 5 Gm NaCl/100 ml and to the presence of cells with abnormal osmotic fragility greater than in the same patient three days or more after splenectomy After splenectomy the distribution curve of osmotic fragility is



[illegible] Emers n C P J [illegible] M d 97 1 38 Jan [illegible] y 1956)

monophasic and symmetrical and remains abnormally increased *Degree of spheroidicity i e of osmotic fragility is* abnormally increased but is distributed as a norm curve about *a mean at which the greatest number of cells hemolyze* The pattern is comparable to the normal but the span exceeds *the normal range* After *splenectomy the abnormal* cells appear to survive normally judging from absence of hemolysis *and also their normal survival when transfused* into a normal person without a spleen In the presence of the spleen *red cell destruction is abnormally rapid in* the disease

with hemolytic anemia such a crisis leads quickly to alarming anemia whereas in individuals whose red cells have a normal life span a transient suppression of erythrocyte production is hardly noticed

Three sisters Monika 8 (Fig 61 top) Marianne 7 (Fig 61 center) and Gabriele 2 (Fig 61 bottom) with previously unrecognized congenital hemolytic anemia became dangerously anemic during the course of the same infection as the result of an aplastic crisis of erythropoiesis Monika and Marianne had had numerous infections before including mumps measles and chickenpox without having an aplastic crisis Principal symptoms of the common infection (which according to complement binding tests probably was due to influenza B virus) were headache prostration and anorexia In all three moderate fever present at the outset subsided within a few days General symptoms disappeared somewhat more slowly especially in Marianne

Finding of microspherocytes and greatly increased osmotic fragility was consistent with a diagnosis of congenital hemolytic anemia Serum bilirubin was slightly increased (1 38 mg / 100 ml) in Monika but was normal in the others Reticulocytes were completely lacking in Gabriele were 0 1% in Monika and 2 4% in Marianne Bone marrows showed deficiency of normal erythroblasts and many large basophilic round cells often in groups Leukocytes in all the children showed a certain leftward shift Monika and Marianne had definite leukopenia with increased plasma cells Coombs test was negative in all Monika and Marianne had definite splenomegaly all three had enlarged livers

The aplastic crisis continued five or six days after hospitalization then reticulocyte levels increased sharply to over 10% In Monika and Marianne reticulocytes remained fixed at this high level but hemoglobin was considerably below normal i e it showed the typical picture of severe congenital hemolytic anemia Even Gabriele s reticulocytes remained at twice normal During the crisis transfusions were administered as a lifesaving measure Additional transfusions were given at the time of discharge The children also received vitamin B_{12} vitamin C and folic acid

The father had had hemolytic anemia in connection with freezing during the war in 1942 the spleen had been removed in 1951 with good results Diagnosis of constitutional hemolytic anemia in his three daughters placed a new interpretation on the supposedly acquired anemia His erythrocytes were found to be typical microspherocytes with decreased osmotic resistance The mother s erythrocytes were normal

Similar observations were reported by Battle (1952) in four brothers aged 7 16 whose father and grandfather had mild hemolytic icterus Three of them had aplastic crisis during the same upper respiratory infection and this was the first indication that they had constitutional hemolytic ane

fractions were altered although the rate constant for P^{32} exchange remained normal Most patients had a lower than normal relative specific activity of ATP with a less marked lowering of the value for 2 3 DPG and a higher than normal value of inorganic phosphate Thus the flux of P^{32} into ATP and 2 3 DPG is smaller than normal in HS cells and the flux into orthophosphate is greater than normal The turnover of P of ATP and 2 3 DPG in the stromal fraction tended to be lower than normal

After splenectomy these abnormalities in intracellular glycolysis persisted Usually incubation of the cells with adenosine largely restored the abnormality to normal Lack of this corrective effect occurred in all members of some families suggesting a familial metabolic difference and the possibility that all patients now regarded as having HS may not be homogeneous

The low P^{32} activity found in stromal ATP of affected cells may be related to the mechanism of sphering The authors suggest that an adequate rate of regeneration of ATP is necessary for maintenance of the cell biconcavity The finding that incubation of HS cells with glucose mannose adenosine or guanosine retards the degree of autohemolysis of incubated HS cells suggests that the biochemical abnormality is related to the principal hematologic findings in this disease The role of the protective substances in this instance may be to enable glycolysis to continue and thus enable the potential energy within the cell to be maintained with ultimate beneficial effect on the multiple factors maintaining cell integrity

Aplastic Crisis in Constitutional Hemolytic Icterus Simultaneous Illness of Three Sisters in Connection with Influenza Infection is described and discussed by K Betke F Debatin and R Sauthoff[9] (Univ of Freiburg) Sudden appearance of anemic crises formerly interpreted merely as hemolytic crises in hemolytic icterus has long been recognized Owren noted that in some cases these aplastic crises were not based on increased hemolysis but on suspended formation of erythrocytes Gasser demonstrated aplastic crises al o in persons without hemolytic anemia In a patient

(9) De t che med W b schr 80 1358 1360 S pt 16 1955

mia Haase (1954) also reported two sisters 10 and 11 in whom congenital hemolytic anemia was first recognized in aplastic crisis during an influenza infection

Hereditary Elliptocytosis Associated with Increased Hemolysis was observed in three children by Hugh W Josephs and Mary Ellen Avery[1] (Johns Hopkins Univ)

CASE 1—Negro male at age 2 months had an episode of hemolytic anemia with an eight fold increase in urobilin excretion increase in osmotic fragility of erythrocytes reticulocytes and characteristic increase in erythroblastic activity of bone marrow Although there was Rh incompatibility there was no history of increased hemolysis before age 2 months and there were no antibodies in serum or on the cells At 3 years 8 months the tip of the spleen was palpable and hemoglobin was 11 Gm erythrocytes 4 400 000 and reticulocytes 3 1% Marked elliptocytosis was seen on the smear Urobilin excretion was increased in both stool and urine

CASE 2—Negro male infant was anemic and resistant to iron therapy To about age 2 hemoglobin tended to assume values determined by current iron intake As he grew older this tendency became less At age 4 hemoglobin was 8 8 Gm without additional iron It is tempting to consider this response a result of his elliptocytosis Although anemia was at first thought due to iron deficiency the relatively high serum iron values and high mean corpuscular volume are not consonant with this diagnosis but suggest a disturbance in hemopoiesis

CASE 3—Negro male was first noticed to be anemic at age 9 months when he had marked hypochromic microcytic anemia and low serum iron content Response to iron with a rise in hemoglobin suggested that he might have had a coincidental iron deficiency Over a four month period without iron he maintained his hemoglobin level at 7 10 Gm During an infection stool urobilin level was over five times normal Reticulocyte count was consistently elevated Erythrocyte survival studies using radioactive chromium (Cr [1]) showed 75% survival after 3 days and only 50% survival after 16 days indicating a significantly decreased life span His general health and weight gain were good and he had no symptoms from the hematologic abnormalities

Hereditary elliptocytosis as exemplified by these cases is a clearly defined entity recognized by presence of elongated erythrocytes in wet preparations and stained smears Although first recognized in 1904 only four reports had appeared by 1925 Even now the condition is little known outside hematology departments and physicians who have happened to encounter it Elongation of the erythrocytes is due to some property inherent in the cells although they do not

(1) Ped 16 741 75 December 1955

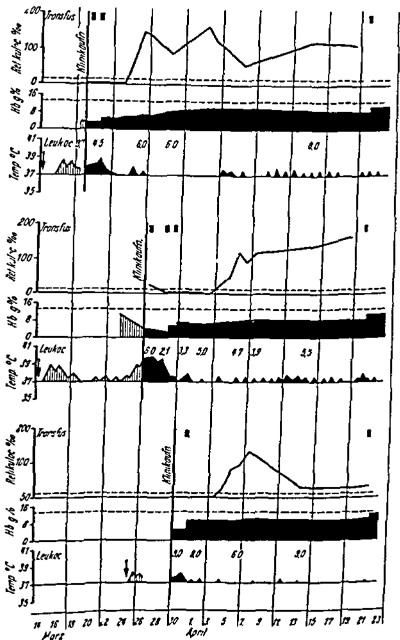
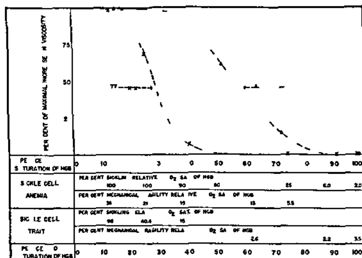


Fig 61 (Court sy of Betk K t al Deutsch med W h schr 80 1358 1360 Sept 16 1955)

crease of plasma viscosity or of rouleau formation as a result of infection might understandably produce extreme erythrostasis This seemed to explain hemolytic anemia capillary congestion thrombotic phenomena and progressive splenic infarction in the disease The authors report extends earlier studies on hematology, blood viscosity and osmotic



F g 62—Effect f d ygen t on on th viscos ty f wh l blood pe ent kl d ll d ryth oc t m h l f g l ty in kl ll em d kl ll t t. (C rt y f H J W t l A M A. A h I t M d 97 145 168 F bru ry 1956)

and mechanical fragilities of the red cells of 23 patients with the sickle cell anomaly in its heterozygous and homozygous forms

Beginning with genetically abnormal hemoglobin chemically defined by Pauling and extending to hematologic findings clinical manifestations and pathologic changes a sequence appears that seems adequate to explain some major aspects of the pathologic physiology of sickle cell anemia Alignment and parallel orientation of the abnormal hemoglobin molecule in its insoluble deoxygenated state result in formation of birefringent hemoglobin tactoids Because of this intracellular molecular orientation the normal bicon

acquire the characteristic shape until the reticulocyte stage or later In several hundred reported cases at least one parent has been a carrier of elliptocytes The condition is not sex linked or confined to any race or region It is easily distinguished from sickle cell anemia although the two conditions have sometimes been confused

The literature makes it clear that hereditary elliptocytosis is a potentially hemolytic disease However in most cases the elliptocytosis is without pathologic significance In other patients there may be hemolytic anemia sometimes sufficient to require splenectomy Between lies an indeterminate group in which there is evidence of hemolysis and compensatory erythropoiesis and in which there may or may not be anemia The authors patients belong to this group

Studies on Destruction of Red Blood Cells X Biophysics and Biology of Sickle Cell Disease In 1927 Hahn and Gillespie clearly defined the anomalous physical behavior of the sickle cell as an abnormality of its hemoglobin when in the deoxygenated state and pointed to affected cells as the primary cause of the characteristic hemolytic anemia They observed that sickling began when oxygen tension of a drop of blood was reduced to about 45 mm Hg provided blood pH was below 7 4 and thus related the sickling phenomenon to the oxygen dissociation curve of hemoglobin

John W Harris Henry H Brewster Thomas Hale Ham and William B Castle (Harvard Med School) note that in 1940 the finding that the apparent hematocrit of deoxygenated portions of sickle cell blood could not be reduced to that of oxygenated portions of the same sample even by prolonged centrifugation led to investigation of the effect of deoxygenation on the viscosity of sickle cell blood When oxygen tension was reduced to 40 mm or less the time required for passing through an Ostwald viscometer became significantly increased It was inferred that because critical oxygen tension for initiation of sickling was close to that of mixed venous blood a vicious cycle of erythrostasis might easily be set up in vivo involving increase in viscosity with resultant decrease in rate of blood flow and consequently further deoxygenation of blood Sickling provided a potential mechanism that if set in motion by a slight in

( ) A M A Arch I t Med 97 145 168 F bru ry 1956

Inst of Health) Methods for hemoglobin analysis include electrophoresis salting out procedures for determination of solubility alkali denaturation and examination of ultraviolet absorption spectrums The hemoglobins differ from each other in their globin portions and differences in the numbers of free sulfhydryl and carboxyl groups have been reported

Hemoglobin A (normal adult hemoglobin) is the only form present in measurable amounts in most human beings after the first seven months of life It is present in some disease states and all carrier states of the hemoglobinopathies It is soluble in salt solutions is labile to alkali denaturation and has an isoelectric point of 6 9 in phosphate buffer Hemoglobin F (fetal hemoglobin) is the first form produced in the fetus A and F are present simultaneously in late prenatal and early postnatal life Production of hemoglobin F may persist in adults with hereditary anemias and in some persons with acquired anemias This form differs from other human hemoglobins by resistance to alkali denaturation in electrophoretic behavior and by a unique ultraviolet spectrum

Hemoglobin S (sickle cell hemoglobin) differs from A and F in electrophoretic mobility markedly reduced solubility in the deoxygenated state and formation of large molecular aggregates and gels in concentrated deoxygenated solutions Hemoglobin C has a greater net positive charge than S (which has a greater charge than A) and a greater solubility than A Hemoglobin D is indistinguishable from S electrophoretically but has a solubility like A Hemoglobin E is unique in behaving electrophoretically like C on the alkaline side and like S on the acid side of their isoelectric points Hemoglobin G has a mobility like that of hemoglobin F electrophoretically but differs from F in lability to alkali denaturation Hemoglobin H has a greater electrophoretic mobility than A at pH 8 6 and a lower isoelectric point than that of A Hemoglobin I has a mobility between those of A and H at pH 8 6 and an isoelectric point between those of A and H Hemoglobin J has a mobility between A and I at pH 8 6 and an isoelectric point between hemoglobins A and I

With respect to clinical manifestations the various states

cave disk form of the erythrocyte is distorted and the cell assumes the sickled form The birefringent sickled erythrocyte is essentially a membrane covered hemoglobin tactoid There is a rough correlation between amount of hemoglobin S present in a cell and the oxygen tension at which tactoid formation and sickling can be induced

Due entirely to the abnormal sickled form of the erythrocytes viscosity of whole blood and mechanical fragility of erythrocytes are significantly increased at decreased oxygen tensions *Figure 62 shows that in sickle cell anemia* the marked increases in viscosity number of sickled cells and erythrocyte mechanical fragility occur in the physiologic range of oxygen unsaturation of venous blood in sickle cell trait the changes take place only at oxygen saturations produced by artificial laboratory conditions

With increase in viscosity of the whole blood a cycle is *initiated in which the factors of stasis lowered pH and* continuing tissue oxygen uptake combine to augment the number of sickled cells and prolong the stasis When red cells after stasis are again released into free circulation a certain proportion have been fixed in irreversibly sickled form and have also become increased in osmotic and mechanical fragilities as a result of such stasis Operation of this cycle seems to *explain in large part clinical manifestations* of the disease i e multiple vascular occlusive phenomena and venous thromboses that underlie tissue changes and hemolytic anemia

In the homozygous state or sickle cell anemia the erythrocytes contain enough abnormal hemoglobin to allow sickling hence increased osmotic and mechanical fragility occur *within the physiologic range of oxygen tensions* Such transfused cells have a short survival time in normal subjects In the heterozygous state (sickle cell trait) the clinical course is essentially benign because sickling although possible with artificially low oxygen tensions in vitro ordinarily fails to occur *in vivo For this reason these cells* survive normally when transfused into normal subjects

Clinical States Associated with Alterations of the Hemoglobin Molecule are reviewed by Harvey A Itano[1] (Nat l

(1) A M A A ch I t Med 96 87 297 Sept mbe 1955

one parent Hemoglobins S A and F are present in most patients although in some only S and F have been found Microcytic sickling cells and mild hemolytic anemia are present

Thalassemia major (Cooley s anemia) results from homozygosity for the thalassemia gene and is characterized by severe chronic microcytic anemia usually fatal in childhood Fetal hemoglobin is constantly present but varies from 12 to nearly 100% the remainder of the hemoglobin is indistinguishable from A Hemoglobin C thalassemia disease may be characterized by the presence of A and C or A C and F hemoglobins and anemia Hemoglobin E thalassemia disease is characterized by the presence of hemoglobins E and F with hematologic abnormalities comparable to those of thalassemia major of intermediate severity

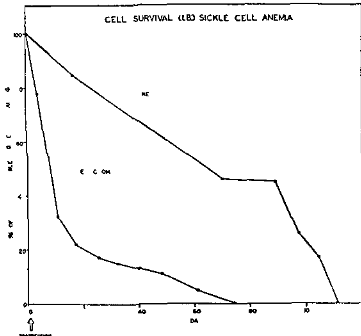
Hemoglobin C disease is due to homozygosity of the gene for C This is the only hemoglobin present in most cases A small fraction of F may be present A mild hemolytic disease is produced Hemoglobin E disease occurs in the presence of E and small amounts of F with microcytic normochromic cells Hemoglobin H produces a disease indistinguishable from thalassemia

There is strong evidence that genes for S and C are allelic There is some evidence to suggest that the thalassemia gene is not allelic to S and C When genes for thalassemia and abnormal hemoglobin are present there is nearly always inhibition of synthesis of normal adult hemoglobin but not of the abnormal type This suggests that the thalassemia gene is allelic with the abnormal hemoglobin genes or that possibly more than one isoallele for thalassemia exists at the abnormal hemoglobin locus Because the hemoglobin molecule is complex it is possible that more than one gene locus controls its total synthesis and hence that several genes both allelic and nonallelic with abnormal hemoglobin locus may produce the thalassemia effect namely inhibition of hemoglobin synthesis

In thalassemia major hemoglobin synthesis appears to be only two to three times the normal rate and in sickle cell disease five to six times normal although patients with hemolytic anemia and normal hemoglobin produce hemoglobin at about seven times the normal rate The mutant hemo

characterized by inherited abnormalities in hemoglobin metabolism can be grouped into asymptomatic carrier states sickle cell disease complex thalassemia and the thalassemia like complex The presence of a single abnormal gene does not ordinarily cause symptoms suggesting the carrier state but may be detected by hemoglobin analysis Off spring of two carriers may have chronic anemia Sickle cell trait occurs in about 9% of American Negroes and is demonstrated by sickling of red cells without anemia Hemoglobins A and S are present in variable amounts usually 25 45% being S Hemoglobin C trait is found in 2 3% of American Negroes with hemoglobins A and C present in approximately a 2 1 ratio An increase in target cells is found Hemoglobin D trait has been reported in two families of European descent No erythrocytic abnormality has been observed and hemoglobins A and D were present Hemoglobin E trait has high incidence in Thailand but is rare in the Western hemisphere It is associated with the presence of A and E but is without hematologic abnormality Hemoglobin G trait has been reported in one West African Hemoglobin I trait has been reported in three generations of an American Negro family and hemoglobin J trait in two generations of an *American* Negro family There were no hematologic abnormalities

Sickle cell disease is characterized by hemolytic disease in the presence of sickling cells and is due to two abnormal genes one from each parent Exceptions may occur when one abnormality is thalassemia or when there is a mutation Sickle cell anemia is due to homozygosity of the gene for hemoglobin S Hemoglobins S and F are found the latter in the range of 0 25% Sickle cell hemoglobin C disease is due to the presence of S and C in nearly equal proportions although fetal hemoglobin may also be present Mild hemolytic anemia is produced and increased numbers of target cells are present *Sickle cell hemoglobin D disease* is a *mild* hemolytic anemia S and D and small amounts of F are present Sickle cell thalassemia disease probably the commonest sickle cell disease among Caucasians, is due to the simultaneous presence of genes for sickle cell hemoglobin and for thalassemia Usually one of the abnormal genes comes from each parent although one case is reported in which both abnormalities were apparently inherited from



F g 63—S rvı l curves of rm l ryth ocytes ın p t t bef d aft m l f n enl ged spl weigh g 750 Gm. (Court y f W t on R J *t al* Am J M d 20 196- 06 F bru ry 1956)

Splenic Aspiration in Eight Cases of Sickle Cell Anemia

C N	I S /1 000 R B oo C L	I S /1 000 Re Bloo C ls	Ra I S B oo /S l
	Blood	Spl en	
1	70	220	1 3
7	5	68	1 14
9	42	378	1 9
14	21	77	1 4
15	6	45	1 7
16	125	244	1 2
17	2	6	1 3
19	2	18	1 9

I S = rre rs'bl kl cell th t cells th t d not rt t th d sc d f rm on gen t on n th p epa tion f blood film

globins thus appear to be produced less efficiently In confirmation of this hypothesis is the fact that the marrow erythroid hyperplasia of thalassemia major is out of proportion to the rate of blood destruction In sickle cell disease the increased rate of hemolysis is due to the presence of sickled cells which in turn have that property because of the tendency of hemoglobin S to aggregate when deoxygenated A slight retardation in the maximal rate of hemoglobin synthesis contributes to the severity of the anemia Consequently abnormal hemoglobin metabolism can cause anemia either by increasing susceptibility to hemolysis or by a decreased rate of hemoglobin replacement

Splenomegaly in Sickle Cell Anemia is discussed by R Janet Watson Herbert C Lichtman and Henry D Shapiro[4] (State Univ of New York New York City) The spleen has long been of special interest in sickle cell anemia because of its variations in size ranging from 1 5 to 1 850 Gm The spleen tends to be enlarged more often in early childhood and shrinks later in life presumably because of repeated infarctions due to thrombosis of enmeshed sickled cells within its vascular bed A few notable exceptions to these trend have been recorded

Relation of degree of anemia and age of patient to size of spleen occurrence of hypersplenism and possible therapeutic value of splenectomy were studied in 115 patients aged 1 54 with sickle cell anemia Palpable spleens were found in 18%—in 33% of patients under 10 and in 10% of those older In seven (six children) splenomegaly was transient In six patients with considerable splenic enlargement anemia was unusually severe although painful crises tended to be less frequent Existence of an extracorpuscular factor in blood destruction was demonstrated in two patients in shortened survival of normal transfused erythrocytes before splenectomy and normal survival afterward (Fig 63) Removal of the spleen resulted in marked clinical improvement and a rise in hemoglobin content so that further transfusions were unnecessary

A relatively high percentage of irreversible sickle cells was found in splenic aspiration compared to that in peripheral blood in eight patients with splenomegaly (table)

(4) Am J Med 20 196-06 February 1956

common with sickle cell trait than in sickle cell anemia Age distribution and life expectancy with the latter may account for the difference

Of three patients with sickle cell hemoglobin C disease with hematuria all had targeting of red cells two had splenomegaly and one had evidence of hemolysis and bone changes None had history of crisis or exhibited the body build and other features of sickle cell anemia All patients with sickle cell trait had typical electrophoretic patterns insignificant fetal hemoglobin levels and no anemia or hemolysis As repeated efforts were made to exclude possible genitourinary or systemic disease or coagulation defects linking hematuria with sickle cell trait in these patients seems justified

Pain was significantly absent during episodes of hematuria All but one had repeated episodes which subsided spontaneously including two on whom nephrectomy was performed after prolonged bleeding and hematuria recurred in both All other patients were treated primarily with bed rest Bleeding occurred more frequently on the left side

Pathologic findings in the two nephrectomized patients included submucosal hemorrhage sickling of red cells in vessel lumens with engorgement of these vessels and of capillaries of the glomeruli and preservation of normal renal parenchyma One had ureteral erosion with underlying hyperemia No thrombosis was seen

Since sickle cell trait is not generally accompanied by the usual stigmas of sickle cell anemia local tissue insult is postulated as the trigger mechanism for vascular injury and subsequent bleeding The kidney is particularly susceptible to effects of shock infection and ischemia and a reasonable assumption is that local changes in the kidney may be responsible for anoxia precipitating the sickling phenomenon with subsequent vascular changes and bleeding The singular susceptibility of kidney and retina to stress may account for the unexpected pathologic changes in an otherwise clinically benign condition

Sicklemia is reported in four cases by Norman Ende Philip Pizzolato and Joseph Ziskind[6] (New Orleans) It has been recognized only recently that the sickle cell trait itself i e

(6) A I t M d 4 1065 1075 M y 1955

This was thought to indicate probable formation and sequestration of these cells in the spleen because such cells may be produced by prolonged incubation of deoxygenated sicklemia blood in vitro

The role of the spleen in sickle cell anemia may be postulated as follows Circulating red cells become sickled in the spleen under conditions of anoxia and stasis irreversibly so if they remain sequestered for a long time Increased mechanical fragility of sickled cells results in hemolysis In most instances sickled red cells (with high viscosity) within the spleen will obstruct circulation in capillaries causing ischemic infarction and subsequent fibrosis and shrinkage However if the sickle blockade is not complete the spleen will enlarge progressively with increasing sequestration and destruction of red cells leading to exacerbation of pre existing anemia if bone marrow production is already maximal With the advent of severe anemia painful crises tend to diminish because there is less opportunity for circulating sickle cells to enmesh and obstruct capillary flow of blood Splenectomy in such cases will diminish the severity of anemia and should be done if the patient is weak and dyspneic and requires blood transfusions This vicious cycle i not constant in patients with splenomegaly but was thought to occur in 6 of 21 patients whose spleens were enlarged

With the discovery of abnormal hemoglobins other than sickle (S) hemoglobin diagnosis of sickle cell anemia should be verified by demonstrating homozygous S hemoglobin by filter paper electrophoresis Both thalassemia sickle cell disease and hemoglobin C sickle cell disease are commonly associated with splenomegaly and may masquerade as atypical instances of sickle cell anemia because of the positive sickling preparation

Gross Hematuria in Sickle Cell Trait and Sickle Cell Hemoglobin C Disease A Zerne Chapman Paul S Reeder Irving A Friedman and Lyle A Baker[5] present five case reports of the former and three of the latter Generally accepted incidence of sickle cell trait in the Negro population is about 8% Incidence of unexplained hematuria associated with this trait noted in 6 of 14 patients available for study is believed to be significant Hematuria apparently is more

(5) Am J Med. 19 773 782 November 1955

The myocardium was essentially normal but coronary veins had numerous clumps of sickled red blood cells Liver and spleen showed marked congestion with sickle cells The brain showed satellitosis with some disorganization of layers of ganglion cells Vessels throughout all brain sections were engorged with masses of sickle cells

After death examination of blood preparations of four living siblings gave negative results for sickling in 24 hours The mother showed 98% sickling in 48 hours She was nearly 70 and seemed in good health She had no history of jaundice swollen joints or symptoms compatible with sickle cell anemia

• [It is questionable how reliable an interpretation can be put on the degree of sickling observed in autopsy specimens as the change may be due entirely to extreme and unphysiologic anoxia after death.—Ed]

Infectious Mononucleosis and Acute Hemolytic Anemia Report of Two Cases and Review of Literature Richard H Thurm and Frank Bassen[7] (Mount Sinai Hosp New York) note that hemolytic anemia in infectious mononucleosis is rare with only 13 cases found in the literature

Case 1—Man 23 first was seen with symptoms of upper respiratory infection and fever He was treated with penicillin but fever persisted and cervical nodes developed Heterophil agglutination titer was 1 3 584 and typical cells of mononucleosis were present on blood smear Hemoglobin content was 15 Gm/100 ml Treatment with chlortetracycline was ineffective and on the twelfth day jaundice and hepatomegaly were noticed Daily temperature spikes to 104 5 F continued and on the thirteenth day hemoglobin level dropped to 9 7 Gm There was reticulocytosis of 4 5% with 2 normoblasts/100 white cells platelets 50 000/cu mm cold agglutinins in titer of 1 64 negative Coombs test 4+ cephalin flocculation and icteric index 39 On the fourteenth day hemoglobin was 8 7 Gm and reticulocytes 9 2% Hypercellular bone marrow with M/E ratio of 0 66 and a three day stool urobilinogen content of 155 mg/24 hours were found There followed subsidence of fever return of hemoglobin levels disappearance of cold agglutinins and normal findings in bone marrow The heterophil titer fell gradually over several months

Case 2—Man 21 with moderately severe Mediterranean anemia had weakness pharyngitis chills and fever Antibiotics cortisone and six blood transfusions failed to correct the anemia Severe illness continued and when seen he was pallid with icteric scleras shotty cervical nodes and marked hepatosplenomegaly Laboratory data revealed severe hypochromic anemia thrombocytopenia and leukopenia with 76% lymphocytes a high proportion of which were typical of infectious mononucleosis Blood smear showed target cells numerous normoblasts and reticulocytosis Heterophil agglutination was positive in a titer of 1 7 168 cold agglutinins 1 320 bilirubin 3 5 mg/100 ml (2 9 mg indirect) and Coombs test results negative Over about five

(7) Blood 10 841 851 Aug t 1955

sicklemia is capable of producing clinical symptoms and pathologic findings Incidence of sickling among Negroes in the United States is estimated at 9% but cases with symptoms attributed to presence of sickle cells are quite rare Bone joint and abdominal pain when left sided with splenomegaly have been reported In one instance multiple infarcts in the spleen were found at operation Hematuria has been a common manifestation of sicklemia and occasionally nephrectomies have been performed because neoplasm was suspected In one patient with cerebral manifestation at autopsy wedge shaped areas of encephalomalacia were found

In four patients observed by the authors since 1949 sicklemia may have been the etiologic agent responsible for signs and symptoms One seen at autopsy showed sickling and congestion of blood vessels and thrombi and evidence of changes secondary to vascular occlusion The others had priapism encephalomalacia and a small bowel infarction Except for one patient with a history of hepatitis all four were well until hospitalization none had anemia or any history of anemia

The possibility that relation of sickling to pathologic changes was coincidental cannot be entirely ruled out In these patients as far as can be determined sicklemia and not sickle cell anemia is represented In three patients genetic history fetal hemoglobin electrophoretic pattern and clinical history were typical of sickle cell trait and not of sickle cell anemia

Negro man aged 46 hospitalized with diagnosis of schizophrenia showed a red blood cell count of 5 600 000/cu mm with hemoglobin value of 15 Gm /100 ml A month later the temperature rose to 103 F and remained between 102 and 105 4 F until death about two weeks later Fever did not respond to antibiotics A week before death red blood cell count was 4 700 000/cu mm hemoglobin and hematocrit values were 13 Gm and 45 ml /100 ml sedimentation rate was 20 mm /minute and leukocyte count 9 900/cu mm with 85% neutrophils

Gross findings at autopsy were distention of colon without obstruction pulmonary atelectasis and infarct congestion of spleen and of vessels of brain and mesentery and small infarct in the right kidney Microscopically infarction of lung and kidney was confirmed Lung vessels were filled with numerous apparently conglutinated sickle cell

stant of S_{20w} = 4 6 Svedberg units Microbiologic assay showed a B_1 content in the complex of 8 5 µg /mg a lower value than the spectrophotometrically calculated quantity thought possibly due to incomplete release of B_1 from the complex by autoclaving Clinical assay in two pernicious anemia patients in relapse produced complete hematologic remission on daily oral doses of 1 2 and 2 4 mg corresponding to 10 and 20 µg vitamin B_1 (microbiologically determined)

• [The two striking clinical responses probably indicate the intrinsic factor activity of the vitamin B protein complex However because preliminary trials in these patients of similar amounts of vitamin B *alone* were not carried out the cl nical tests are open to criticism especially as the chemically determined amounts of vitamin B given daily were 17 6 and 35.2 µg respectively Such controls were employed by the authors of the succeeding article —Ed.]

Preparation of Highly Purified Intrinsic Factor Several investigators have achieved partial purification of intrinsic factor by applying one or two fractionation steps William L Williams Leon Ellenbogen and Raymond G Esposito[9] (Pearl River N Y) describe further purification of intrinsic factor from an ammonium sulfate precipitated fraction of which 13 mg was an effective daily dose Successive steps were digestion with proteolytic enzymes alcohol fractionation and finally ultrafiltration The ultrafiltration residue fraction proved effective in pernicious anemia patients in relapse at a daily dose of 1 or 2 mg with vitamin B_1 Electrophoresis and ultracentrifuge studies of this fraction showed that the major component had a molecular weight of about 5 000 It contained 15 2% glucosamine and 11 8% nitrogen Confirmatory analysis showed that it contained 14% hexosamine hydrochloride By a differential colorimetric method about half the hexosamine was determined as glucosamine hydrochloride and the remainder was presumably chondrosamine hydrochloride

Clinical tests for activity were considered valid only if the pernicious anemia patient in relapse failed to respond to 10-20 µg vitamin B_1 /day for 10 days before receiving vitamin B_1 plus intrinsic factor and if the reticulocyte peak was near the average expected for parenteral therapy of pernicious anemia with liver extract Degree of purification of

(9) P oc Soc E pe B 1 & M d 87 400 405 N embe 1954

months time hemolysis continued despite treatment with cortisone and return of heterophil agglutinins toward normal Splenectomy was performed and the spleen showed foci of foam cells around arterioles extensive blood cell formation fibrosis of pulp and follicles hemosiderosis and erythrophagocytosis Liver biopsy showed only a large amount of iron in parenchymal cells Postoperatively he maintained a hemoglobin level of 8 9 Gm /100 ml without further transfusions • [Cause of the hemolytic anemia is obscure and hypersplenism is favored by the authors because of the absence of red cell abnormalities and the presence of splenomegaly in both patients especially in Case 2 in which it may have been in part due to Mediterranean anemia In three reported cases the Coombs test was positive Hemolysis of red cells by direct action of the virus or by low titers of cold agglutinins is unlikely Autohemolysins have been reported only once in the hemolytic anemia under discussion —Ed]

PERNICIOUS AND OTHER NUTRITIONAL MACROCYTIC ANEMIAS

Clinically Active Vitamin B_1 Protein Complex was prepared by Jørgen Gad Andresen[8] (Copenhagen) Using the Escherichia coli test as a measure of intrinsic factor activity the author prepared hog gastric mucosa concentrates with 25 times the coli activity of the starting material Clinical testing of this concentrate combined with vitamin B_1 showed that intrinsic factor activity had been concentrated at least 25 times

To a commercial intrinsic factor concentrate (bendogen) with a vitamin B_1 binding capacity of about 500 coli units per milligram of protein the calculated amount of vitamin B_1 was added and the preparation then purified by salt precipitation acid precipitation adsorption and dialysis A complex of high molecular weight of an intense red color and a vitamin B_1 content of 14 7 μg /mg was obtained Vitamin B_1 content of the complex was calculated on the basis of the absorption at 550 mμ Absorption spectrum of this complex showed a maximum at 362 mμ instead of 361 mμ for pure vitamin B_1 The greater maximum found at 278 mμ was considered to corroborate the presence of a protein component in the complex Ultracentrifugation showed a nearly symmetrical single peak with a sedimentation con

(8) Acta pharmacol et tox 10 41 45 1954

tion of liver extract revealed typical findings of mild megaloblastic anemia After five monthly injections of 100 µg vitamin B red cell count improved and serum B concentration rose to normal To tal volume of fasting gastric juice was 20 50 ml continuous aspira tion produced an average of 100 ml/hour without histamine Hista mine test meals gave normal results for acid and pepsin secretion His tologically gastric mucosa showed normal distribution quality and quantity of mucous zymogenic and parietal cells Fat balance vita min A oral glucose tolerance curves and gastrointestinal x rays were normal The patient was unable to absorb test doses of radioactive vitamin B unless given with 50 cc of normal human gastric juice The patient s gastric juice contained minimal intrinsic factor activity when tested in a case of pernicious anemia as did that of his father A brother clinically normal absorbed radioactive vitamin B normally

The parents were first cousins The mother s brother had died of carcinoma of the stomach at about age 30 but her other three siblings were alive and well There was no history of anemia or neurologic dis ease in any other member of either side of the family Patient was one of six children one died at age 11 of Hodgkin s disease another at 11 weeks of strangulated hernia The others aged 29 25 and 17 were well but the 17 year old like the patient could not read or write The father had mild typical addisonian pernicious anemia with achy lia gastria and gastric atrophy The mother and brother aged 17 were normal

In 6 of 16 possible cases of pernicious anemia in infancy collected in 1951 there was a family history of megaloblas tic anemia and in four instances the parents were related As the mother and father of the present patient are first cousins he possibly is homozygous for pernicious anemia which might explain early onset of the disease Though it was impossible to demonstrate any abnormality of B_1 me tabolism in the mother she might also carry the gene which might cause the disease later Alternatively it is possible that some other genetic factor besides the abnormal gene must be present to cause anemia at an early age and that the mother carries this factor but not the gene for per nicious anemia

Absorption of Radioactive Vitamin B_1 in Nonanemic Patients with Combined System Disease presents a pre sumptive means of differentiating this condition from other similar neurologic disorders according to Irwin M Aria Leonard Apt and Myron Pollycove (Boston) To demon strate the confusion that may arise in such cases they re

(2) N w E gl d J M d 253 1005 1010 Dec 8 1955

the ammonium sulfate fraction represented an increase in intrinsic factor potency over that of desiccated hog stomach of about 150 fold and of the ultrafiltration residue fraction of about 1 000 fold With the exception of a preparation from human gastric juice reported by Welch and Heinle to be effective at 0 6 mg daily in one patient the ultrafiltration residue fraction at a daily dose of 2 mg is the most potent intrinsic factor preparation yet reported Prusoff *et al* showed that vitamin P_1 binding is nonspecific and cannot be used as an assay for intrinsic factor Low vitamin B_1 binding capacity of the ultrafiltration residue fraction supports this theory Ascribing all the binding capacity of ultrafiltration residue fraction to the low molecular weight component would require over 1 000 molecules of this component to bind 1 molecule of vitamin B_1 Vitamin B_1 binding apparently is not a property of intrinsic factor Latner *et al* have reported on a highly active material with a molecular weight of 15 000 20 000 Proteolytic enzymes (trypsin and chymotrypsin) were not as here used in its preparation

Addisonian Pernicious Anemia without Gastric Atrophy in a Young Man D L Mollin S J Baker and I Doniach[1] (Postgrad Med School London) report reinvestigation of a youth aged 18 who had formerly been observed by Langmead and Doniach (1937) with pernicious anemia as an infant

Boy aged 13 months showed at first study red blood cell count of 2 500 000/cu mm hemoglobin value 50% and reticulocytes 1 3% Red cells varied markedly in size and shape and the Price Jones curve was similar to that seen in pernicious anemia He was treated with crude liver extract (2 ml intramuscularly daily) Reticulocytes rose to peak of 19% but increase in red cells and hemoglobin concentration was slow When iron was also given red cell count rose in four weeks to 5 000 000 and hemoglobin concentration to 90% He was continuously treated with liver extract except for a period at age 3 when he became severely anemic but responded when liver extract given parenterally was reinstated Hemoglobin concentration was usually about 80% (11 8 Gm /100 ml) In recent years he was in good health took a good mixed diet and had no diarrhea or bowel dysfunction

At age 18 he was sturdy but small sexually underdeveloped and mentally retarded Spleen was palpable 5 cm below the costal margin Laboratory studies still showed mild macrocytic anemia and serum B_1 concentration was subnormal Bone marrow 28 days after injec

(1) B t J H mat 1 278 290 J ly 1955

viewed subsequent histories and response to therapy in eight patients reported by Suh and Merritt in 1938 as having combined system disease without pernicious anemia The study indicated that vitamin B_1 deficiency was not related to the neurologic disease in any of them

The authors report personal observations in four patients with combined system disease (table) At time of diagnosis none showed evidence of major hematologic disorders or had had previous treatment with vitamin B_1 liver extract or folic acid Three of these patients received vitamin B_1 for 4 96 months before determination of intrinsic factor activity by radioactive vitamin B_1 One studied before and after vitamin B_1 treatment had a serum concentration of 32 µµg /cc before treatment In all treatment produced subjective and objective neurologic improvement

These nonanemic patients with combined system disease and four treated patients with pernicious anemia had less than 19% hepatic deposition of oral radioactive test dose (lowest in controls aged 67 86 was 40%) In seven of the eight patients deposition was under 9% This presumably represents virtually complete absence of intrinsic factor activity which was further demonstrated in nonanemic patients with combined system disease by failure of their gastric juice to increase hepatic deposition of an oral test dose given to patients with treated pernicious anemia Patients in both groups demonstrated significant increases in hepatic deposition of oral test dose given with normal human gastric juice Each patient showed some objective neurologic improvement after vitamin B_1 treatment and no adverse progression of neurologic signs was noted in a follow up of 2 96 months

Megaloblastic Anemia Associated with Surgically Produced Gastrointestinal Abnormalities is reported by James A Halsted[3] (Syracuse N Y) Sometimes resulting from total gastrectomy or from operations that produce a blind loop of bowel subsequent to intestinal anastomosis this type of anemia is usually due to deficiency of vitamin B_1 although the mechanism of the deficiency is different Using a method measuring fecal excretion after oral administration

(3) C l f rn M d 83 12 17 S pt mbe 1955

CLINICAL AND LABORATORY DATA ON NONANEMIC PATIENTS WITH COMBINED SYSTEM DISEASE

Patient	Sex	Age	Chief Symptom	Duration of Symptoms (Months)	[illegible]	Neurologic Signs before Treatment			Hematologic Findings before Treatment		
						Deep Tendon Reflexes	Plantar Responses	Vibratory Sense	Hemoglobin Gm./100 cc	Peripheral Blood Morphology	Bone Marrow Morphology
W R	M	8	[illegible] of feet	17	Absent	+++ ankles & knee jerks	Bilateral flexor	[illegible] wrists & knees	14 0	Normal	—
W T	M	61	Numbness of hands & feet	6	Absent	++++ ankle & +++++ knee jerks	Bilateral extensor	[illegible] wrists & knees	14 0	Rare [illegible] macrocyte	Rare [illegible] & giant band form
P B	F	66	Numbness of hands & feet	9	Absent	++++ ankle & knee jerks	Bilateral flexor	[illegible] knees & right wrist	13 5	Normal	—
A L	M	66	Unsteady [illegible]	18	Absent	+++ ankle & knee jerks	[illegible] right [illegible] on left	[illegible] wrists & knees	13 5	Rare [illegible] macrocyte	Occasional [illegible]

tient excreted most of the test do e even when given with intrinsic factor so differing from patients with pernicious anemia in whom intrinsic factor has a positive effect on absorption During administration of the antibiotic there was a pronounced decrease in fecal excretion of radioactive vita

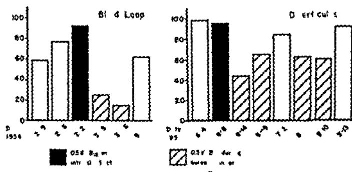


Fig 64 —Fecal tio f Co[60] t m n B two patients w th t t b l (Court y of Hal t d J A C l t Med 83 1 21 S pt mbe 1955)

min B_{12} in each case One interpretation is that the blind loop serves as a site for luxuriant bacterial growth with resultant bacterial competition for B_{12} the competition being decreased by antibiotic treatment The megaloblastic anemia of fish tapeworm infestation also responds to elimination of the worm However the author believes that the mechanism in his patients is likely more complex than bacterial competition

Absorption of Vitamin B_{12} in Gastrectomized Rats G M Watson and H W Florey[4] (Oxford) found that when normal rats were fed 0 005 µg vitamin B_{12} labeled with Co^{60} average excretion in feces was 66 5% of the dose After the same dose of labeled vitamin B_{12} rats from which the distal glandular half of the stomach had been excised excreted an average of 93 8% When given an extract of the glandular portion of rat stomach with vitamin B_{12} such gastrectomized rats excreted an average of 69 5% A dialyzed filtrate of pig pyloric juice did not consistently reduce amount of vitamin B_{12} excreted (table)

(4) B J E pe I th 36 479-436 O t ber 1955

of 0.5 μg radioactive vitamin B_{12}. Halsted studied its absorption in 12 patients with total gastrectomy and in 3 with megaloblastic anemia associated with intestinal anastomosis and blind loop formation.

In normal persons the absorption of the test dose of vitamin B_{12} ranged from 43 to 81%. In the 12 patients with total gastrectomy (1 with megaloblastic anemia) essentially the entire test dose was recovered in the stools. When normal human gastric juice was given with it, normal absorption occurred, suggesting that the exclusive site of intrinsic factor origin in man is in the stomach. The rarity of occurrence of megaloblastic anemia following gastrectomy is explained by (1) limited survival after operation in most cases (three year survival in postoperative gastric carcinoma about 20%), (2) interval before development of anemia, the normal liver containing enough B_{12} for a theoretic four years use, (3) incomplete gastrectomy, particularly that leaving a portion of cardia, and (4) frequency of prophylactic therapy with preparations containing folic acid or even B_{12} and concentrated intrinsic factor.

To the 79 cases found in the literature Halsted adds three in which megaloblastic anemia is associated with an intestinal stricture or surgically produced anastomosis that leaves a blind loop of gut. The anemia produced is indistinguishable from pernicious anemia except that hydrochloric acid and intrinsic factor can be demonstrated in the stomach. Because steatorrhea is uncommon and both fat and glucose adsorption is normal, failure of intestinal absorption is not likely as a cause.

Of the three patients presented, one had mild megaloblastic anemia and combined system disease four years after an intestinal resection, the second had megaloblastic anemia 10 years after several operations to correct internal fistulas following appendicitis and the third had a resection of two feet of ileum with cecum with end to side anastomosis of ileum to hepatic flexure following volvulus complicating diverticulosis of the small intestine. After measurement of B_{12} excretion each was given either aureomycin or achromycin and the tests repeated.

The results (Fig 64, one case omitted) show that each pa

Mandema and W B Castle[5] report experiments in which percentage excretion of radioactivity in feces of normal and totally gastrectomized rats following administration of a single dose of 0 015 μg Co^{60} B_1 was determined by scin tillation counting Gastrectomized rats were not used until at least 10 days after operation and only if in apparent good health

In 11 normal rats a significant fraction (about half) of the test dose of Co^{60} B_1 in water was usually absorbed as in ferred from excretion of radioactivity In 14 gastrectomized rats there was apparently no absorption When 2 ml normal human gastric juice was used as a source of intrinsic factor absorption of vitamin B_1 did not improve nor was fecal ex cretion diminished when 6 ml normal human gastric juice in divided doses an hour apart was given Administration of 4 mg and even of 20 mg of a preparation of hog stomach mucosa was also ineffective in decreasing excretion of ra dioactivity When whole rat stomach homogenized in water was given in a dosage of half a stomach to a gastrectomized rat absorption of vitamin B_1 apparently became normal When the dose was decreased to a tenth of a stomach per rat effect on fecal excretion was only slight When 3 ml rat gastric juice was given average reduction in fecal radio activity resembled that obtained with half a homogenized rat stomach When half a homogenized rat stomach was giv en after heating on a boiling water bath for seven minutes effectiveness appeared greatly diminished

The rat like man secretes intrinsic factor largely if not exclusively into the stomach but sources of human and hog intrinsic factor possess little or no activity in the rat The ob servations of Watson and Florey that in the rat secretion of intrinsic factor is probably confined to the distal secretory portion of the stomach were confirmed Thus when half the distal glandular portion of a rat stomach homogenized in water was given to a gastrectomized rat fecal excretions were 54 72% average 60% of radioactivity administered Similar experiments with the proximal portion of the rat stomach showed no effect on fecal excretion

Though inhibitory effect of nonspecific binding of vita

(5) Proc Soc Exp Biol & Med 91 3 833 February 1956

Much individual variation in ability to absorb vitamin B_{12} was seen in both normal and gastrectomized rats that received rat stomach extract Possible explanations for in consistent results with a preparation of pig pyloric juice are (1) quantity (3 ml) may have contained too little intrinsic factor to produce a consistent effect or a small dose may be effective only when other unknown variables are favorable (2) responses may have been masked by vitamin B_1 already present in pyloric juice (3) possibly there are species dif ferences in intrinsic factors and pig intrinsic factor may not be effective in the rat Latner (1955) mentioned observations

EXCRETION OF ORALLY ADMINISTERED VITAMIN B , BY GASTRECTOMIZED RATS

	V t B i t 1 (d se t		V t m B f t t h t P ce f d se reted		V t n B nd p g t l ju 6lt P ent f lose reted		
R t	1 (m l	2 d t l	R t h l	B t t	R t h t	B t h	Rat 13
1		1	0	81	9	—	—
	1	3	12	3	79	—	—
1	84	—	13	57	9	90	—
4	0	5	72	82	84	83	90 8
	9		1	81	6	—	93 93
		—	—	—	—	83	89
	87	—	—	—	—	—	94
8	3	—	—	—	—	—	93
1	97 8 per cent		69 5 per cent		83 2 per cent		
R x	83 99		51 93		63 9		

on normal and gastrectomized rats affording evidence that intrinsic factor has some degree of species specificity Me chanical causes or some deficiency depending on loss of gas tric juice was postulated as the possible etiologic factors causing the ulcers encountered in the stomach remnants in some animals

The method used did not prove satisfactory for assay of pig pyloric juice for intrinsic factor but extracts of the ani mals own gastric mucosa were satisfactory Hence this tech nic might be useful in studies relating to the mode of action of intrinsic factor to its quantitative relations with vitamin B_1 and to the effects of systemic or intestinal disturb ances on absorption of vitamin B_1

Enhanced Absorption of Vitamin B_{12} in Gastrectomized Rat by Rat Intrinsic Factor H O Nieweg A Arends F

cious anemia serum significant cell increases were obtained with addition of folinic acid but not with vitamin B_1 Both vitamin B_1 and folinic acid appeared to accelerate the conversion of megaloblasts to normoblasts in differential counts of stained smears of such cultures No enhancing effect of intrinsic factor on the activity of B_1 in suspension cultures of megaloblasts was observed The effect of folinic acid could be blocked by colchicine and folinic acid could reverse the inhibitory effects of amethopterin This indicated that folinic acid acted in suspension cultures by stimulating mitosis

Megaloblasts could be produced from normoblastic marrows by culturing them in pernicious anemia serum or in normal serum in the presence of amethopterin

• [The many experiments performed require study of the original article In view of the apparent species specificity of intrinsic factor at least for the rat the lack of any maturing effect of intrinsic factor of animal origin on human bone marrow megaloblasts can perhaps not be considered contradictory to the positive effects of human gastric juice reported by Callender and Lajtha (Blood 6 1234 1239 December 1951) —Ed]

Occurrence of Gastric Cancer among Patients with Pernicious Anemia at Boston City Hospital is analyzed by Norman Zamcheck Ernest Grable Allyn Ley and Leona Norman Reported rates vary widely (0 16 14 9%) In this series of 1 222 patients frequency varied according to the sample selected from less than 1% to over 11% Approximately 10% had gastric cancer by the time they died or left the clinic (presumably dead)

This high rate of cancer warrants the routine use of screening tests which requires a long continued program The average duration of pernicious anemia before onset of gastric cancer was found to be about seven years The ideal screening method must be simple and inexpensive enough to permit frequent repetition i e at intervals of three to six months Standard x ray examinations and gastroscopy require the services of highly trained physicians and hence are prohibitively expensive The authors propose the following program routine stool examinations for occult blood at monthly intervals examination of gastric cytology every three to six months and follow up x ray and gastroscopic study in suspicious cases

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(7) N w E gl d J M d 25 1103 1110 J 30 1955

min B_1 by human and hog intrinsic factor preparations cannot be excluded negative results with these are consistent with the speculation of Chow and his associates that intrinsic factor may possess species specificity *In this connection* it is interesting that Toporek and his associates found that in contrast to plateau effect of hog stomach preparations progressively more Co^{60} B_1 was absorbed in patients with pernicious anemia when normal human gastric juice was used as a source of intrinsic factor

Effect of Various Metabolites on Growth of Marrow Cells in Vitro was studied by Harold T Swan Edward H Keiner Jr and Morris Silverman[6] (New York Univ) particularly their effects on megaloblastic marrows

METHOD —Buffy coat explants from megaloblastic marrow aspirates of patients with pernicious anemia in relapse were grown on chick plasma clots using the double cover slip technic Medium was of chick embryo extract balanced salt solution and human serum from patients with pernicious anemia normal adults and placental veins Samples were examined at 1 2 3 4 and 7 days Similar growth was obtained from marrow particles smeared on glass slivers submerged in the same medium in slanted tubes and later air dried and stained Suspension cultures were prepared by injecting marrow aspirate into siliconized McCartney bottles containing balanced salt solution One bottle served as control others had metabolites and antimetabolites added in desired concentrations in 0 1 ml volume The cultures were incubated 24 96 hours at 37 C Resuspension was made and total nucleated cell count/cu mm was made to compare with initial counts Metabolites used were vitamin B in 0 0007 0 03 µg /ml concentration gastric juice from normal subjects intrinsic factor of animal origin folinic acid 0 1 1 µg /ml and folic acid 1 and 5 µg /ml Amethopterin diluted to 0 05 0 2 µg /ml and colchicine 1/100 000 were the antimetabolites used

Vitamin B_{12} appeared to stimulate cell growth in cultures grown on clots and to convert megaloblastic hemopoiesis to *normoblastic in cultures grown on glass* Growth in pernicious anemia serum alone was less vigorous than in normal or pernicious anemia serum plus vitamin B_1 in which growth was exuberant At seven days fibroblast formation was much more advanced in cultures containing vitamin B_1 *Folinic* acid in pernicious anemia serum had about the same effect as vitamin B_1

In suspension cultures of megaloblastic marrows in perni

(6) Blood 10 735 71 July 1955

cy of specific hemopoietic factors in body tissues Mild deficiency with transitional forms only (intermediate megaloblasts) and/or a number of giant stab cells in the marrow occurred much oftener than classic fully developed megaloblastic anemia Variable normoblastosis was always present in these marrows Coexisting iron deficiency either was present or developed during specific response to treatment of the megaloblastic anemia in many cases Findings suggested the presence of a hemolytic component in three patients

Bone marrow findings support the concept that the megaloblast is an abnormal variant of the normoblast which may undergo all degrees of transition depending on the severity of the responsible deficiency or deficiencies Dietary deficiency was present in most instances In contrast to reports from other centers in temperate climates one patient responded to vitamin B_1 orally and three responded to vitamin B_{12} parenterally Four patients in whom vitamin B_1 therapy failed subsequently responded to folic acid Six responded to folinic acid There were no folic or folinic acid failures Spontaneous remission occurred in three instances Serial bone marrow study was the most accurate single measure of response to therapy Minimal effectual dosage was greater and response to therapy was slower in pregnancy than is usual in addisonian pernicious anemia

In temperate climates megaloblastic anemia associated with pregnancy and the puerperium may result from deficiency of folic acid vitamin B_1 and possibly an unknown factor The best and most consistent response to therapy was obtained with folic and folinic acids These studies suggest that mild deficiency of these substances occurs more frequently than commonly believed Disappearance of this type of anemia from wards and clinics of this hospital since June 1953 when antepartum daily supplements of 4 5 µg vitamin B_1 and 3 0 mg folic acid were initiated may have more than passing significance

Megaloblastic Anemia Associated with Adult Scurvy Report of Case Which Responded to Synthetic Ascorbic Acid Alone is presented by Alexander Brown[9] (Royal Infirm Glasgow)

Man 57 with hepatic cirrhosis and mild evidence of dysfunction

(9) B t J H em t 1 345 351 O t b 1955

The accuracy of the cytologic method has been demonstrated Patients with pernicious anemia are ideal subjects because absence of acid peptic juice permits recovery of well preserved exfoliated cells Simple gastric lavage through an ordinary stomach tube is most practicable for routine office screening The collected aspirate is promptly centrifuged at high speed for 20 30 minutes and smears are immediately fixed in equal parts of 95% ethanol and anesthetic ether Fixed slides may be sent to a reputable laboratory for staining and interpretation Both the guaiac test and the simple method of aspiration cytology may be performed by technicians with minimal professional supervision

Cells have been described in gastric smears that appear to be characteristic of the gastric atrophy of patients with pernicious anemia Persistent absence of these characteristic cells on repeated examination raises doubt of the existence of pernicious anemia and may preclude the need for further screening or even for further therapy of pernicious anemia This subject requires further study as does the suggestion that transitional forms may exist between characteristic cells of gastric atrophy and those of gastric cancer

Megaloblastic Anemia of Pregnancy and Puerperium is reported by Louis Lowenstein Charles Pick and Newell Philpott[8] in 18 patients seen at Royal Victoria Montreal Maternity Hospital 1949 52 Another patient was studied during a previous pregnancy in 1948 Routine antepartum hematologic studies were used to detect anemia

There were no pathognomonic clinical symptoms or signs Only occasionally could diagnosis be established from hematologic findings In most instances cytologic studies of bone marrow comprised the only reliable diagnostic method Comparison of bone marrow findings in these patients with those in normal pregnant and puerperal women with iron deficiency and posthemorrhagic anemias in both pregnant and nonpregnant women and with miscellaneous anemias of pregnancy established that in the pregnant or puerperal woman the presence of megaloblasts intermediate megaloblasts and/or macrogranulocytes in bone marrow permits the diagnosis of megaloblastic anemia Degree of megaloblastosis reflects the degree and duration of deficien

(8) Am J Obst & Gyne 70 1309 1337 December 1955

cy of specific hemopoietic factors in body tissues Mild deficiency with transitional forms only (intermediate megaloblasts) and/or a number of giant stab cells in the marrow occurred much oftener than classic fully developed megaloblastic anemia Variable normoblastosis was always present in these marrows Coexisting iron deficiency either was present or developed during specific response to treatment of the megaloblastic anemia in many cases Findings suggested the presence of a hemolytic component in three patients

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(9) B t J H m t 1 345 351 O t be 1955

was known a year previously to have a hemoglobin level of 13 7 Gm./100 ml a red cell count of 4 700 000 and normoblastic marrow erythropoiesis He was hospitalized because of dyspnea anorexia and weight loss of five months duration Examination showed malnutrition massive ecchymoses and petechiae on the lower limbs hepatomegaly and moderately increased capillary fragility He had 3% reticulocytes 6 5 Gm hemoglobin 1 850 000 red cells 5 600 white cells and 170 000 platelets/cu mm The bone marrow showed megaloblastic erythropoiesis There was histamine fast achlorhydria A liver biopsy demonstrated cirrhosis Since no hematinic therapy had been given he

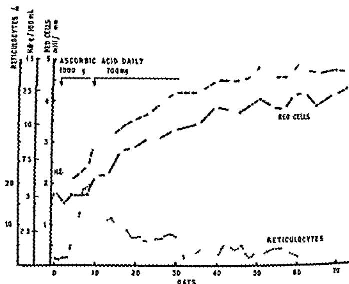


Fig 65 — Peripheral blood response to administration of ascorbic acid
(Courtesy of Brown A Brit J Haemat 1 345 351 October 1955)

was placed on a diet low in vitamin C and animal protein A vitamin C saturation test was begun but saturation did not occur until 7 9 Gm ascorbic acid had been given over 10 days thereafter he received 700 mg daily Figure 65 shows the striking hemopoietic effects Repeated bone marrow examination showed reversion to normoblastic marrow by the 19th day Serum B_{12} levels during treatment ranged from 160 to 325 µµg /ml and folic acid content was 0 33 mµg /ml One year later remission was maintained

Brown calls attention to the variability of the association of anemia and scurvy and to the possibility in many cases of associated dietary defects No well authenticated case of megaloblastic anemia in an adult with response to ascorbic acid alone was found Some authors have produced megalo

blastic anemia in monkeys with ascorbic acid deficient diets which were also low in folic acid The anemia did not develop unless the liver content of folinic acid was low In the case reported although ascorbic acid most probably caused the hematologic recovery Brown believes it likely that some defect of folic acid metabolism existed Although folic acid assay after vitamin C treatment was started was normal the patient differed from the usual scorbutic patient in having multilobular hepatic cirrhosis Since the liver probably serves to transform folic to folinic acid it is conceivable that a defect in liver function combined with ascorbic acid deficiency might lead to the situation described and be reversible by ascorbic acid

• [Jandl and Gabuzda (Proc Soc Exper Biol & Med 84 452-455 1953) have shown that the hemopoietic effect of folic acid is potentiated by ascorbic acid in nutritional macrocytic anemia associated with clinical scurvy in patient with Laennec s cirrhosis If ascorbic acid is required for the conversion of folic acid to its hemopoietically active form a limiting deficiency of either folic acid or ascorbic acid could theoretically cause and so be therapeutically effective in the presence of a less severe deficiency of the other —Ed]

Megaloblastic Anemia Due to Phenytoin Sodium In 1954 Badenoch described two patients on phenytoin sodium therapy who had megaloblastic anemia and normal vitamin B_{12} absorption and five other cases have since been described G M S Ryan and J W B Forshaw[1] present their observations on two patients with megaloblastic anemia and normal gastric acidity who were taking phenytoin sodium as well as data from the hospital records of others A review of the records of 56 patients with megaloblastic anemia who were hospitalized during a four year period revealed that none were on phenytoin sodium therapy Blood examinations on 102 epileptic patients who had been taking phenytoin sodium for several years revealed no instance of this type of anemia One possible case of megaloblastic anemia associated with phenytoin sodium was revealed however by examination of the laboratory records of 140 mental hospital patients who had hemoglobin below 70% This patient was not investigated sufficiently to rule out pernicious anemia or steatorrhea but in view of her age (27) and good nutritional state these diagnoses seem unlikely

The authors two patients were carefully studied and phen

(1) Brit M J 2 242 43 July 23 1955

ytoin sodium was the probable etiologic factor, since no known cause of megaloblastic anemia was evident In view of the rarity of this condition (2 among 58 cases of megaloblastic anemia or 3 4%) and the excellent response to phenytoin sodium in epileptics its use is not contraindicated However when megaloblastic anemia develops another anticonvulsant drug should probably be substituted

Of the 10 cases so far described 7 were treated initially with vitamin B_{12} but only 4 showed a good response There was a good response in two patients treated with folic acid initially and in three who received folic acid after vitamin B_{12} had failed Badenoch showed that serum vitamin B_{12} level and its absorption were normal in his two patient and yet one responded well to treatment with vitamin B_{12} Because of these findings the pathogenesis of the condition is not clear and will require further study

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HYPOCHROMIC ANEMIA

Pyridoxine Responsive Anemia in Human Adult is reported by John W Harris Richard M Whittington Russell Weisman Jr and Daniel L Horrigan[2] (Western Reserve Univ)

The patient was first hospitalized in 1947 at age 27 for hypochromic anemia Principal signs and symptoms during the subsequent course could be directly attributed to decreased hemoglobin level and were abolished with repeated transfusions Patient s appetite remained good dietary intake was adequate and he maintained a constant weight Therapeutic agents tried at various times included purified and crude liver extracts bio hepulin (from pregnant mare s liver) brewers yeast tablets ferrous sulfate cobaltous chloride pteroylglutamic acid ascorbic acid leucovorin cyanocobalamin pantothenic acid cortisone fresh human plasma and combined vitamins including A D thiamine riboflavin and niacin in large doses All proved ineffective in producing hematologic or subjective improvement

By August 1955 he had received a total of 113 units of whole blood At that time erythrocytes numbered 2 860 000 with 5 9 Gm hemoglobin hematocrit 22% and 25 500 leukocytes Mean corpuscular volume was $66\mu^3$ and mean corpuscular hemoglobin concentration 27% Erythrocytes were definitely abnormal in size and shape with frequent bizarre forms and target cells Transfusion of 300 ml packed red cells

(2) Proc Soc Exper Bi l & M d 91 427-432 M h 1956

was given on the same day as pyridoxine hydrochloride 200 mg intramuscularly daily was started After four doses there was subjective improvement and on the seventh day reticulocytes had risen to 50 8% Hematocrit and hemoglobin rose rapidly to 49% and 13 Gm respectively and leukocytes decreased to 9 200 Tibial pain pedal edema and nocturia which had been bothersome for some time disappeared Pyridoxine was discontinued after 5 doses two months later

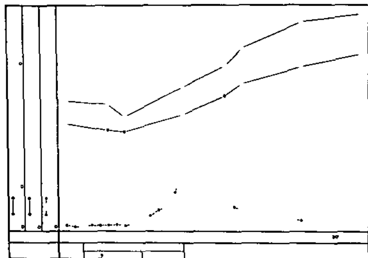


Fig 66—L k f p t 1 mg py d t m 1 ly d ly w th b q t pon t 10 mg d 1 Th 1t pt pha load g t t w do d y — S d 17 (Court y f H J W t l P oc Soc E p B l & M d 91 4 7-43 M h 1956)

hematocrit had fallen to 27% and hemoglobin to 7 8 Gm No significant reticulocyte response occurred after parenteral administration of 1 mg pyridoxine daily (Fig 66) after eight days dose was increased to 10 mg and a reticulocyte peak of 17 7% on the seventh day was followed by rapid rise in hemoglobin and hematocrit Three oral loading tests of 4 Gm 1 tryptophan before pyridoxine therapy and during the course of 1 mg daily indicated urinary abnormalities of tryptophan metabolism which were completely normalized by the 10 mg daily do e Serum iron level was changed by therapy from 170 µg /100 ml to 67 µg and iron binding capacity of 184 to 214 µg /100 ml protein iron saturation of 92% was reduced to 31%

Despite extensive empirical use of pyridoxine as a therapeutic test agent for many conditions its essential role in

ytoin sodium was the probable etiologic factor since no known cause of megaloblastic anemia was evident In view of the rarity of this condition (2 among 58 cases of megaloblastic anemia or 3 4%) and the excellent response to phenytoin sodium in epileptics its use is not contraindicated However when megaloblastic anemia develops another anticonvulsant drug should probably be substituted

Of the 10 cases so far described 7 were treated initially with vitamin B_1 but only 4 showed a good response There was a good response in two patients treated with folic acid initially and in three who received folic acid after vitamin B_1 had failed Badenoch showed that serum vitamin B_1 level and its absorption were normal in his two patients and yet one responded well to treatment with vitamin B_1 Because of these findings the pathogenesis of the condition is not clear and will require further study

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(2) P oc Soc Exper B ol & M d 91 427 432 M rch 1956

deficient or defective (3) Iron binding capacity in plasma was disturbed (defect or blocking of metal binding beta$_1$ globulin)

Results in these patients indicated that absence of the stomach does not result in poor absorption of well ionized iron but that as suggested by the intestinal biopsy studies of Paulson and Harvey sooner or later after total resection progressive atrophic enteritis affects iron absorption Changes in intestinal mucosa are due to several factors Altered bacterial content with altered digestive demands superimposed on already accelerated peristalsis in the small intestine leads to chronic inflammation that in turn also influences elimination These changes account for development of iron deficiency anemia after total gastrectomy besides there is usually a gradually decreased oral iron intake which itself can cause mucosal atrophy

• [These results based on single acute tests in individual patients can scarcely be considered as more than suggestive of their conclusions —Ed.]

Oral Iron Compounds Therapeutic Comparison was made of ferric hydroxide ferrous sulfate ferrous succinate and ferrous gluconate in doses of 210 mg elemental iron given daily to 80 patients by D J O Sullivan P G Higgins and John F Wilkinson[4] (Manchester Royal Infirm) Ferric hydroxide in the small daily dose was unsatisfactory which is not surprising because the normal therapeutic dose of this preparation contains 1 200 2 400 mg. elemental iron per day whereas here only 210 mg was used Little difference was noted in effectiveness of the three ferrous compounds that proved satisfactory but the slight differences favored ferrous succinate and sulfate a re ult surprising in view of Haler s conclusions (1952) and the accumulated trade literature Haler used a somewhat similar dose of ferrous sulfate and a much smaller dose of ferrous gluconate so that the utilization coefficient of the latter tended to gain Also the ferrous gluconate preparation he used contained among other supplements ascorbic acid which appreciably increases absorption of iron whereas in the sulfate group vitamins were given only when vitamin deficiency appeared likely

Patients refractory to one oral preparation were refrac

(4) La t 2 48 485 S pt 3 1955

human hemopoiesis has been demonstrated only in one hydrocephalic infant maintained on a synthetic diet lacking pyridoxine Present observations indicate that abnormal hemopoiesis (associated with abnormalities in metabolism of tryptophan and iron) can occur in the adult secondary to a naturally occurring alteration in pyridoxine metabolism Since dietary intake of pyridoxine (3 mg daily) in this patient apparently was normal an absorptive defect or a metabolic aberration may account for the findings The nature of the alteration and its role in hemopoiesis are unknown

• [A new variety of nutritional anemia in man! It closely resembles that induced by pyridoxine deficiency in swine extensively studied by Wintrobe et al (Bull Johns Hopkins Hosp 72 1 25 January 1943) This condition should be suspected when hypochromic anemia with a high serum iron level is present and thalassemia can be excluded In our experience with one such patient daily oral therapy with 20 mg pyridoxine was without effect whereas the same amount given parenterally on advice of Dr Harris produced reticulocyte responses and increases in hemoglobin on two occasions —Ed]

Absorption of Iron Perorally after Total Gastrectomy was studied by O Rainer and S Zollner[3] (Klagenfurt) in 17 patients with normal and anemic blood findings Each was given eight lozenges of ferronicum equivalent to 176 mg ferrous iron Serum iron was determined before (during fasting) and two five and seven hours after ingestion of iron A polyvinyl catheter was introduced into a vein through a cannula under local anesthesia and was left in place for withdrawal of blood throughout the seven hours Besides the iron loading test x rays of the digestive tract total serum proteins with analyses by electrophoresis glucose tolerance tests and stool analyses were carried out Iron binding capacity was also determined in some cases

Eleven patients with total gastrectomy had a normal blood picture Most of these had had gastrectomy because of tumor but three had benign ulcers Only one had a definite recurrence (metastatic) at the time of study As expected iron absorption curves varied considerably With one exception the fasting serum iron levels were either within or under half of the normal value In five patients the serum iron increased during the test by 100 mg /100 ml In the other patients the following possibilities were recognized (1) Iron saturation was normal (2) Absorption in intestine was

(3) Wien klin Wchnschr 67 735 737 Sept 16 1955

nously injected radioiron is influenced by the size of the iron stores and that less radioiron appears in circulating erythrocytes when the stores are increased probably due to the low specific activity of the iron circulating through the marrow Thus a slow rate of incorporation of radioiron in hemoglobin might indicate that the iron stores are filled despite a low serum iron level Lack of increase in concentration of iron transporting globulin in serum also agrees with this hypothesis

The finding that cortisone treatment in Case 1 increased the rate of incorporation of intravenously injected radioiron in circulating erythrocytes is difficult to interpret There was not however any improvement of the anemia when the patient was under cortisone therapy

Apparently different degrees of the disturbance of iron metabolism may exist In a boy aged 3 the fundamental abnormality seemed to be the same although not to the same degree since he exhibited some though poor response to iron therapy

Treatment of Iron Deficiency Anemia is described by Daniel H Coleman Alexander R Stevens Jr and Clement A Finch[6] (Univ of Washington) In the normal person the amount of iron absorbed and lost from the body each day is exceedingly small In certain periods of life body iron requirements are increased the most important of these is infancy Then existing iron stores are rapidly depleted and a deficient diet can soon cause iron deficiency Once a full complement of body iron has accrued the adult is independent of iron intake and becomes iron deficient only through blood loss Iron stores are exhausted before anemia appears If any question in diagnosis from usual laboratory tests exists failure to find hemosiderin on direct examination of marrow will establish the diagnosis of iron deficiency It is important to confirm the diagnosis by specific therapy and to determine cause of iron depletion

Ferrous salts have an absorption of 10 15% in the usual oral therapeutic doses In the adult the dose of ferrous sulfate (0 2 Gm tablets) or ferrous gluconate (0 3 Gm tablets) is 1 or 2 tablets three times daily after meals (total daily dose

(6) Blood 10 567 581 J 1955

tory to all but responded to iron parenterally Intolerance manifested as nausea and vomiting was observed after ferrous sulfate in 13% after ferrous succinate and gluconate in 4%

Incidence of intolerance varies directly with dosage Since ferrous sulfate in doses of 210 mg produces adequate hematologic response there is much to be said in favor of its routine use in this dosage corresponding roughly to 0 6 Gm daily The relatively small proportion of patients intolerant to these smaller doses should then be tried on one of the other organic iron preparations If they are still intolerant therapy should be given parenterally Ferrous sulfate is much cheaper than ferrous gluconate or succinate and equally efficacious Hence it maintains its position as a satisfactory therapeutic agent

• [This article indicates the desirability of further re evaluation of the practical effectiveness of doses of ferrous iron somewhat smaller than those customarily employed —Ed]

Refractory Sideropenic Anemia in Childhood Due to Error of Iron Metabolism Rolf Zetterstrom and Simone Delava[5] (*Stockholm*) *present two cases in which* findings indicated that anemia was caused not only by poor iron absorption from the gastrointestinal tract but by a more generalized disturbance of iron metabolism not secondary to infection or other disease Case 1 follows

Girl 7 had a diagnosis of hypochromic anemia and was under observation over two years She exhibited typical general sideropenic symptoms There was no evidence of occult bleeding no symptoms of steatorrhea and the concentration of hydrochloric acid in the gastric juice was normal The bone marrow showed changes typical of long standing sideropenic anemia The anemia failed to respond to peroral treatment with high doses of iron for almost 1½ years and there was no reticulocyte peak or rise of hemoglobin level after intravenous iron therapy Studies with radioactive iron showed that the serum iron level was extremely low but that the iron binding capacity was normal Absorption of iron from the alimentary tract was defective and intravenously injected radioiron was utilized for hemoglobin synthesis at a slow rate There was rapid plasma iron turnover

The authors postulate that the rapid disappearance of radioiron given intravenously was due to a high rate of exchange between the plasma iron and the iron in the depots It has been demonstrated that the distribution of intrave

(5) Blood 10 245 1255 December 1955

the total calculated course has been completed In infants and children 20 mg can be given initially followed by injections of 50 mg if the first is well tolerated Reported incidence of reactions is 5 35% Serious reactions have occurred with large doses and one fatality has been reported but danger other than subjective discomfort is considered negligible within the dosage limits outlined

Chronic toxicity from iron loading in the form of hemochromatosis is a consideration with any effective parenteral iron preparation A toxic amount of tissue iron is that in excess of 25 Gm Since there is no reason to exceed 5 Gm saccharated iron in any one course of therapy the hazard is negligible If depletion of iron stores is verified by marrow examination before further iron therapy is given no hazardous accumulation of iron will result during multiple courses

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OTHER ANEMIAS

Pathogenesis of Anemia in Patients with Carcinoma with attention to the role of hemolysis as measured by routine examinations and the Ashby red cell survival technic and by the rate of erythropoiesis both by marrow aspiration and by ferrokinetic studies using Fe^{59} was reported on by George A Hyman and Jane E Harvey (New York)

Forty five patients with widely disseminated biopsy proved carcinoma (of various types) who had not had recent overt blood loss radiotherapy chemotherapy or transfusion were studied Of 26 of these 1 showed a moderate increase in hemolysis 14 a slight increase and 11 no change on routine tests Ashby type studies were done 19 times in 17 patients with various carcinomas 15 studies showed a moderate to marked increase in the rate of destruction of transfused cells (Fig 67) In one patient the curve was about normal and in three only a slight increase in red cell destruction occurred In two patients repeat studies revealed a further increase in the rate of hemolysis with progression of the disease Of 11 studies on patients with noncarcinomatous neoplasms all

(7) Am. J Med. 19 350-356 Sept mbe 1955

of 220 440 mg iron) Elixir of ferrous sulfate is recommended for infants and small children 4 ml three times daily representing 110 mg iron For children over age 6 or for adults twice this dose is used An intake in excess of 0 4 Gm ferrous iron is needed only when continued brisk blood loss or relatively poor absorption makes response to the usual dose inadequate Although effective oral dose of iron could be reduced if combined with 1 Gm ascorbic acid this has little practical value in view of the efficacy of iron alone It has been suggested that cobalt may accelerate response to iron but it cannot be recommended in view of possible toxicity

The result of adequate therapy is highly predictable A significant response is defined as an increase in hemoglobin of 2 Gm /100 ml or more (rise in hematocrit of over 5) within three weeks If response does not occur in that time an explanation for failure should be sought The most likely reasons are (1) incorrect diagnosis (2) complicating disease inhibiting response i e infection or uremia (3) concurrent blood loss in excess of that compensated for by iron absorbed (4) medication not taken by patient and (5) failure of absorption of ingested iron Most patients resistant to oral iron therapy have a widespread absorptive defect such as occurs in sprue

Indications for parenteral administration of iron in order of importance are (1) intolerance of iron orally (2) gastrointestinal disease which may be adversely affected by iron orally (3) for creation of iron stores and (4) poor absorption of iron (exceedingly rare) Several colloidal iron preparations are available for parenteral therapy The widest experience has accumulated with saccharated oxide of iron Suggested therapy consists of a trial course of injections to total 500 mg in adults 250 in children and 100 in infants A reticulocyte response or rise of 2 Gm of hemoglobin in three weeks is taken as confirmation of diagnosis, and full replacement therapy is then given In the adult a single injection usually 20 mg iron/ml should be given over three to five minutes Initial dose should not exceed 50 mg second injection 100 and *third 200 mg If no symptoms of intolerance* have occurred the last dose can be given each 24 hours until

As no mention of tests for possible occult blood loss is made one wonders if the authors excluded this hazard to the interpretation of such studies —Ed.]

Myelophthistic Anemia in Cancer of Breast is notoriously refractory to treatment and is an ominous prognostic sign according to Charles D West Allyn B Ley and Olof H Pearson[8] (New York) who observed 18 cases during one year

The most common peripheral blood findings were normocytic anemia immature leukocytes and erythrocytes thrombocytopenia reticulocytosis and a normal white cell count In 8 of 14 cases tumor cells were found in marrow aspirations Usually a differential count could not be done on the marrow aspirate because of insufficient marrow elements but when a count was possible either a normal differential was obtained or there was a slight increase in erythroid elements Increased hemolysis was observed clinically in only one case

Temporary remission in myelophthisic anemia secondary to cancer of the breast was observed in 7 of 17 cases after treatment with castration androgen or cortisone therapy or hypophysectomy In responsive cases survival averaged 4 8 months in unresponsive cases 1 1 months

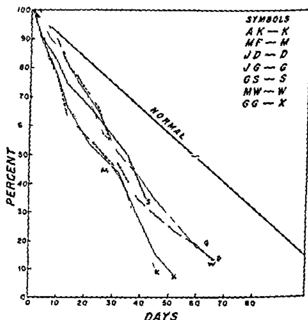
Of eight patients examined at autopsy liver enlargement attributed to metastases was present in six. In two of five with splenomegaly enlargement was attributed to myeloid metaplasia in the others it seemed primarily due to metastases In seven cases in which slides were examined for myeloid metaplasia all showed marked displacement of normal marrow elements by metastatic cancer and had myeloid metaplasia of the spleen microscopically Four patients had myeloid metaplasia of the liver one in the lymph nodes and another in the kidney

Erythroblastic Hypoplasia Associated with Thymic Tumor and Myasthenia Gravis Report of a Case is presented by Jack C Weinbaum and Robert F Thompson[9] (Ann Arbor Mich) with a review of eight previously reported instances of similar severe anemia in patients with thymic neoplasms with and without myasthenia gravis

(8) Am J Med 18 923 931 J 1955
(9) Am J Cli P th. 25 761 769 J ly 1955

showed a moderate to marked increase in red cell destruction

In all 45 patients bone marrow aspirate showed tumor cells Only 4 marrows showed decreased cellularity 35 showed approximately normal and 6 increased cellularity Plasma iron level was depressed in 31 of 45 patients in association with depressed plasma iron binding globulin a nor



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mal saturation percentage was noted in 14 patients Intravenous plasma iron disappearance rates red cell iron renewal rate and percentage of Fe [9] utilized for erythropoiesis indicated a normal or increased state of erythropoiesis The authors conclude that a major factor in anemia of advanced cancer is an increase in hemolytic activity Most patients showed normal or increased erythropoietic activity which was inadequate to prevent development of anemia

• [This high incidence of a shortened red cell survival is not typical of other studies of patients with moderately advanced metastatic carcinoma.

folic acid iron and multiple vitamins orally Erythrocyte progenitors were depressed in the sternal marrow the new nucleated red cells present were young forms with basophilic cytoplasm and were in various stages of degeneration The granuloctyic series was well represented and megakaryocytes were present in normal numbers Blood transfusions were discontinued after a total of 2 500 ml Three days before death hemoglobin was 2 6 Gm/100 ml A few mall petechiae were noted on trunk and extremities

At autopsy the bone marrow was hyperplastic consisting almo t entirely of granulocytic cells Erythrocytic progenitors were absent In contrast to bone marrow three weeks previously megakaryocytes were also markedly reduced in number Anatomic diagnoses were erythroblastopenic anemia thymic tumor (thymoma) associated with myasthenia gravis (clinically) hemosiderosis of spleen liver mucosa of small intestine and bone marrow

It is of interest that in more common classic types of aplastic anemia associated with thymic lesions the lesions varied Conversely all patients with only erythroblastic hypoplasia of the bone marrow had similar thymic neoplasms This suggests a relation between certain thymic tumors and erythroblastic hypoplasia of bone marrow Of the six cases in which a thymoma has been surgically removed the anemia was cured in two relieved in two and unaffected in two

Cobaltous Chloride in Treatment of Certain Refractory Anemias Paul P Weinsaft and Leo H T Bernstein[1] (V A Center Martinsburg W Va) report on eight patients with chronic normocytic normochromic anemia who in many instances had required repeated transfusions and had failed to respond to other therapy Four had chronic glomerulonephritis one chronic pyelonephritis two chronic rheumatoid arthritis and one Hodgkin s disease Pretreatment hematocrits ranged from 23 35% Daily administration of 0 12-0 16 Gm cobaltous chloride in divided doses was adequate for satisfactory response and maintenance of attained hematologic levels In all patients increases in hematocrit hemoglobin values and erythrocyte count were observed Hematocrits ranged from 31 to 50%

Side effects—mild abdominal distress and slight nausea—were minimal and easily controlled by gradually increasing the dosage Cobalt salts do not appear unduly toxic to the animal organism In man parenteral administration of large

(1) Am J M Sc 230 264 269 S pt mbe 1955

In 1928 Matras and Priesel described a thymic tumor consisting of epithelioid cells and cells resembling lymphocytes found at autopsy in a woman 62, who had a three year history of marked anemia believed during life to be pernicious anemia Davidsohn (1941) reported the occurrence in a woman 58 of severe anemia and a mediastinal mass visible by fluoroscopy Initial red blood cell count was 1 600 000 no reticulocytes were present Marrow showed depression or hypoplasia of erythropoietic elements The patient died 19 months after her first hospitalization At autopsy a firm globular encapsulated mass was found in the upper mediastinum histologic diagnosis was lymphoepithelioma of the thymus In 1945 Humphreys and Southworth reported aplastic anemia terminated by removal of a mediastinal tumor in a woman 58 without myasthenia gravis Sternal marrow biopsy showed mild hypoplasia After removal of the tumor the blood showed a sharp reticulocytosis with return of the erythrocyte count to normal There was no postoperative recurrence of anemia or tumor which was believed to be of thymic origin Autopsy 10 months after operation showed widespread hemachromatosis and lobar pneumonia Ross and associates (1954) reported a simultaneous occurrence of benign thymoma and refractory anemia in two women Anemia in both was associated with a marked decrease of erythropoietic activity in bone marrow They cited two additional cases of refractory anemia in which some improvement followed resection of a thymoma—one in a man 48 with myasthenia gravis Chediak *et al* (1953) described a man 47 with severe anemia and complete aplasia of erythropoietic elements of bone marrow whose blood findings returned to normal after removal of a thymoma that was demonstrated radiographically

Woman 76 had had diabetes mellitus myasthenia gravis and anemia for several years when hospitalized in 1951 Since she had previously responded to treatment for pernicious anemia she was given 15 μg vitamin B intramuscularly for 13 days but reticulocytes failed to respond Hyperglycemia persisted despite dietary restrictions and increasing protamine zinc insulin A mass possibly thymoma was discovered roentgenologically during an acute episode of bronchopneumonia which responded to antibiotic therapy No hematologic improvement followed liver extract intramuscularly and

healthy persons in this age group may have slightly reduced arterial O_2 saturation polycythemia may coexist with slight to moderate anoxemia caused by pulmonary disease (2) Patients with polycythemia occasionally have arterial anoxemia which is considered to be secondary to polycythemia itself

In a man 63 arterial blood studies showed anoxemia suggesting that he had secondary polycythemia Lung volumes distribution of inspired air distribution of pulmonary capillary blood alveolar-capillary diffusion and mechanics of breathing were within normal limits Hypoventilation was a major factor there was CO_2 retention resting alveolar ventilation was abnormally low in relation to O_2 consumption anoxemia could be relieved by voluntary hyperventilation. By exclusion diagnosis of specific depression of the medullary respiratory center was made As long as the patient lives it cannot be known whether the nerve lesion is primary or secondary to thromboses related to polycythemia Lack of response to treatment and lowering of arterial saturation at follow up nine months later indicated progression of the central nervous system depression

In 24 patients with polycythemia vera vital capacity was 80% or more of the predicted value in 23 maximum breathing capacity was 80% or more in 17 and arterial P_{CO_2} was 43 mm Hg or less in all but 2 The ratio of resting ventilation to total lung capacity in 11 patients was normal in all but 1 Distribution of inspired gas was measured in 19 and was normal in all Arterial O_2 saturation measured during exercise in nine decreased below the resting value in only one Uptake of CO (test of diffusion across alveolar capillary membranes) was normal in all four patients tested These studies indicate that serious derangement of pulmonary function is exceptional in polycythemia vera

Data on the degree of polycythemia associated with chronic pulmonary disease are shown in the table Patients with right to left shunts with congenital heart disease or pulmonary hemangiomas were excluded in these red blood cell count hemoglobin and hematocrit values are uniformly high unless hemorrhage has occurred In the patients with chronic pulmonary disease hemoglobin rarely exceeded 16 5 Gm / ml and hematocrit usually was not over 55% Factors which limit polycythemic response in patients with anoxemia caused by chronic pulmonary disease may be (1) increased arterial P_{CO_2} values which occur in many patients

doses has produced nausea vomiting and temporary fall in blood pressure in animals tremors and convulsions have been observed Tinnitus and nerve deafness have been reported in four patients but complete recovery followed when cobaltous chloride was discontinued Five cases of thyroid hyperplasia with hypothyroidism apparently resulting from prolonged cobalt therapy in Negro children with sicklemia have also been reported All evidence of thyroid deficiency disappeared within several weeks after withdrawal of the drug

Cobalt appears to be valuable in treatment of anemias secondary to chronic disease Though the underlying pathologic state was not affected all patients showed tangible improvement concomitant with that of hematologic values

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POLYCYTHEMIA

Anoxemia Secondary to Polycythemia and Polycythemia Secondary to Anoxemia Originally O Ratto W A Briscoe J W Morton and J H Comroe Jr (Univ of Pennsylvania) believed that this differential diagnosis could be made solely by careful measurements of arterial O_2 saturation Theoretically uncomplicated polycythemia vera should not lead to arterial anoxemia because diffusion across normal alveolar capillary membranes permits transfer of enough O to saturate fully even twice the usual number of red blood cells/unit of blood/unit time Furthermore simple pulmonary vascular congestion believed to accompany polycythemia should not lead to decrease in diffusing capacity of the lungs In most patients with severe polycythemia arterial O saturation is normal The authors studies confirmed this and they therefore regarded normal arterial O saturation at rest and during exercise in a polycythemic patient as strongly suggesting primary disease The logical corollary, that reduced arterial O_2 saturation indicates that polycythemia is secondary to anoxemia is questionable on several grounds (1) Patients with polycythemia vera are usually over 50 and

(1) Am. J Med 19 958-965 December 1955

fer from those in polycythemia vera Early in the investigation they also appeared to differ sufficiently from secondary polycythemia (of hypoxemia) to warrant separate classification but later studies of two additional patients have characterized this condition as a form of secondary polycythemia due to inadequate pulmonary ventilation presumably because of the mechanical barrier created by fat Since arterial oxygen saturation is only slightly depressed it is postulated that only the most sensitive individuals respond with polycythemia which would explain the rarity of the condition

There is no increase in immature cells white blood cells or platelets in peripheral blood and the bone marrow does not display hyperplasia Splenomegaly is absent and moderate doses of radiophosphorus do not influence blood cell count The arterial oxygen saturation is only slightly depressed and cyanosis is absent The condition may occur with cardiorespiratory liver and renal dysfunction Weight reduction without other therapy may be curative

Polycythemia with Fibroids Herbert W Engel and Karl Singer[4] (Michael Reese Hosp) present a case similar to one described by Thomson and Marson in 1953 in which fibromyomas of the uterus were associated with polycythemia and after hysterectomy and bilateral salpingo oophorectomy the polycythemia rapidly disappeared

Woman 39 had complained of severe headaches and blurring of vision for years The uterus was irregularly enlarged to the size of a 10 week pregnancy Hemoglobin was 21 4 Gm /100 cc. red blood cell count 6 800 000 and hematocrit 61% The leukocyte and platelet counts were normal as were also the retinal vessels Lips and oral mucous membranes appeared cyanotic There was no lymphadenopathy and the cardiovascular system showed no abnormality The tip of the spleen was palpated 2 cm below the costal margin The liver was not enlarged A mass arising out of the pelvis and extending toward the umbilicus was identified as the uterus which contained multiple subserous nodules Adnexa appeared to be normal Hematologic abnormalities were completely alleviated by total hysterectomy and bilateral salpingo-oophorectomy

No explanation can be offered for these phenomena but they are deemed sufficiently interesting to alert the profession into considering such an interrelationship

• [Possibly as in the obese patients just described the etiologic rela

(4) J A M A. 159 190 191 Sept. 17 1955

HEMOGLOBIN AND HEMATOCRIT VALUES IN PATIENTS WITH CHRONIC ANOXEMIA CAUSED BY PULMONARY DISEASE

No Patients	Arterial O Saturation %		Hemoglobin Gm /100 Ml		Hematocrit % Cells	
	Mean	Range	Mean	Range	M	Range
5	46 2	26 8—59 0	13 8	9 2—16 4	47 6	3[illegible]5—56 0
9	75 7	70 2—79 9	13 9	9 8—18 8	48 6	37 6—63 0
29	86 6	80 —89 9	14 2	9 2—16 8	46 8	35 0—57 0
71	92 7	90 2—95 3	13 6	9 8—17 1	43 5	3[illegible]0—54 [illegible]

with uneven ventilation in relation to pulmonary capillary blood flow and (2) chronic pulmonary infection On clinical grounds alone if venous arterial shunts are excluded diagnosis of polycythemia vera is likely in any patient who has a hematocrit greater than 60% and hemoglobin value exceeding 17 Gm /100 ml

Polycythemia Associated with Obesity is discussed by Max H Weil[3] (Univ of Minnesota) whose interest was aroused by a massively obese patient with polycythemia and related metabolic disturbances that disappeared completely with weight reduction alone A group of Mexican authors reported polycythemia in 12 (5%) of 240 obese patients with hematocrits as high as 77%

Weil subsequently reviewed 260 cases of clinical obesity and found polycythemia (hemoglobin 19 Gm /100 cc or above sometime during hospitalization) in two males and two females In two of the four patients polycythemia was transient and coincidental to the major illness One a woman had clinical symptoms of erythremia but was discharged against advice before the polycythemia could be carefully studied The fourth patient was a man 28 (5 ft 10 in tall 254 lb) whose hemoglobin was 19 8 Gm /100 cc red blood cell count 6 100 000 and hematocrit 56% Despite therapy his weight remained practically unchanged and four courses of radioactive phosphorus did not affect the polycythemia Transient relief was afforded by repeated phlebotomies In Weil s series the incidence of persistent polycythemia was 0 8% 10 times the over all incidence (0 08%) among 150 000 hospital admissions

The clinical findings in obesity related polycythemia dif

(3) J A M A 159 159 1595 Dec 4 1955

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There is no increase in immature cells white blood cells or platelets in peripheral blood and the bone marrow does not display hyperplasia Splenomegaly is absent and moderate doses of radiophosphorus do not influence blood cell count The arterial oxygen saturation is only slightly depressed and cyanosis is absent The condition may occur with cardiorespiratory liver and renal dysfunction Weight reduction without other therapy may be curative

Polycythemia with Fibroids Herbert W Engel and Karl Singer[4] (Michael Reese Hosp) present a case similar to one described by Thomson and Marson in 1953 in which fibromyomas of the uterus were associated with polycythemia and after hysterectomy and bilateral salpingo oophorectomy the polycythemia rapidly disappeared

Woman 39 had complained of severe headaches and blurring of vision for years The uterus was irregularly enlarged to the size of a 10 week pregnancy Hemoglobin was 21 4 Gm / 100 cc. red blood cell count 6 800 000 and hematocrit 61% The leukocyte and platelet counts were normal as were also the retinal vessels Lips and oral mucous membranes appeared cyanotic There was no lymphadenopathy and the cardiovascular system showed no abnormality The tip of the spleen was palpated 2 cm below the costal margin The liver was not enlarged. A mass arising out of the pelvis and extending toward the umbilicus was identified as the uterus which contained multiple sub erous nodules Adnexa appeared to be normal Hematologic abnormalities were completely alleviated by total hysterectomy and bilateral salpingo-oophorectomy

No explanation can be offered for these phenomena but they are deemed sufficiently interesting to alert the profession into considering such an interrelationship

• [Possibly as in the obese patients just described the etiologic rela

(4) J A M A 159 190 191 Sept. 17 1955

HEMOGLOBIN AND HEMATOCRIT VALUES IN PATIENTS WITH CHRONIC ANOXEMIA CAUSED BY PULMONARY DISEASE

No Patients	Arterial O Saturation %		Hemoglobin Gm /100 Ml		Hematocrit % Cells	
	Mean	Range	Mean	Range	M	Range
5	46 2	26 8—59 0	13 8	9 2—16 4	47 6	32 5—56 0
9	75 7	70 2—79 9	13 9	9 8—18 8	48 6	37 0—63 0
29	86 6	80 —89 9	14 2	9 2—16 8	46 8	35 0—[illegible]
71	92 7	90 2—95 3	13 6	9 8—17 1	43 5	32 0—[illegible]

with uneven ventilation in relation to pulmonary capillary blood flow and (2) chronic pulmonary infection On clinical grounds alone if venous arterial shunts are excluded diagnosis of polycythemia vera is likely in any patient who has a hematocrit greater than 60% and hemoglobin value exceeding 17 Gm /100 ml

Polycythemia Associated with Obesity is discussed by Max H Weil[3] (Univ of Minnesota) whose interest was aroused by a massively obese patient with polycythemia and related metabolic disturbances that disappeared completely with weight reduction alone A group of Mexican authors reported polycythemia in 12 (5%) of 240 obese patients with hematocrits as high as 77%

Weil subsequently reviewed 260 cases of clinical obesity and found polycythemia (hemoglobin 19 Gm /100 cc or above sometime during hospitalization) in two males and two females In two of the four patients polycythemia was transient and coincidental to the major illness One a woman had clinical symptoms of erythremia but was discharged against advice before the polycythemia could be carefully studied The fourth patient was a man 28 (5 ft 10 in tall 254 lb) whose hemoglobin was 19 8 Gm /100 cc red blood cell count 6 100 000 and hematocrit 56% Despite therapy his weight remained practically unchanged and four courses of radioactive phosphorus did not affect the polycythemia Transient relief was afforded by repeated phlebotomies In Weil s series the incidence of persistent polycythemia was 0 8% 10 times the over all incidence (0 08%) among 150 000 hospital admissions

The clinical findings in obesity related polycythemia dif

(3) J A M A 159 159 1595 Dec 4 1955

and six months pregnant. She was well and her blood count was normal

Polycythemia in this patient could not be explained on the basis of poor oxygenation of the blood or of an arteriovenous shunt anywhere in the body particularly within the tumor There was no evidence of endocrine imbalance Splenomegaly and leukocytosis which usually accompany polycythemia rubra vera were never present

Budd Chiari Syndrome Complicating a Case of Polycythemia Vera According to Robert N Brown Joseph W Pidgeon and Harry A Johnson [6] only 9 of 123 cases of Budd Chiari syndrome reported in the literature were associated with polycythemia vera Diagnosis of this syndrome was made ante mortem in only about 1 case in 10 At Los Angeles County General Hospital only 2 cases were observed in 50 000 autopsies None was seen at White Memorial Hospital in over 200 000 admissions and 3 800 autopsies Stanford University Hospital reported 5 in 11 979 autopsies and from 1910 to 1939 there were 20 at the Mayo Clinic 16 of which were discovered at autopsy To 1948 only seven cases had been reported in children

The Budd Chiari syndrome may be acute or chronic The acute form has a rather sudden onset with vague abdominal pains often with nausea vomiting abdominal guarding and even shock Ascites is quite common Patients go into coma and delirium and die in one to four weeks Onset in chronic cases is more gradual with indigestion epigastric distress and rapidly recurring ascites The liver is enlarged in all cases and usually the spleen also Jaundice is minimal or absent The disease may last for years but apparently is always fatal most patients die from liver failure

The cause of the disease is obscure It is characterized by acute and chronic thrombosis in hepatic veins In some cases obstruction is in the inferior vena cava primarily and extends into hepatic veins in others it occurs at the osteum of the hepatic veins and in some is confined to hepatic veins themselves Besides polycythemia vera the syndrome has been associated with sickle cell anemia pregnancy leukemia and primary and metastatic tumors in the upper abdomen

Woman 37 was hospitalized because of progressive abdominal

(6) Calif rnia M d. 83 37 39 J ly 19 5

tion is to restricted ventilatory capacity because of the increased volume of the abdominal contents The mucous membranes appeared to be cyanotic but no determination of the percentage oxygen saturation of the arterial blood was made —Ed]

Polycythemia Associated with Renal Tumor is *reported* by Q B DeMarsh and W J Warmington[5] (Seattle) They cite a case reported by Forsell (1946) in which blood and marrow findings of polycythemia returned to normal after removal of a right hypernephroma but recurred 14 months later when a tumor developed in the left kidney At autopsy this proved to be hypernephroma Videbaek (1950) found 2 cases of hypernephroma at 35 autopsies on patients with polycythemia and described a patient with proved polycythemia and hypernephroma still alive at the time of his report *Polycythemia disappeared after nephrectomy* but this patient had also received 6 mc P^{32}

Girl 7 was hospitalized in March 1944 because of polycythemia discovered at age 5 during routine immunization of a group of children At that time her hemoglobin was *20 5 Gm /100 ml* erythrocytes 9 200 000 and leukocytes 6 500 She had had severe intermittent headaches and a plethoric appearance for several years History included a severe fall at about 3 years of age which caused unconsciousness *for about 15 minutes but no apparent injury* Weekly bloodlettings and x ray therapy to long bones (*1 200 r*) had not been beneficial On examination hemoglobin was 19.2 Gm erythrocyte count 7 850 000 and leukocyte count 8 750 The right kidney was enlarged and in grossly abnormal position when she was upright but renal function was normal Polycythemia was then regarded as genuine polycythemia rubra vera After discharge frequent venesections were needed to relieve severe headaches Later she also had episodes of dizziness nervousness vomiting delirium blurred vision back pain and hemetemesis (*for which no cau e could be found*) *In March* 1946 bilateral sympathectomy was performed in hope of relieving the polycythemia but on two subsequent admissions in 1947 and 1949 her condition and laboratory findings remained essentially unchanged

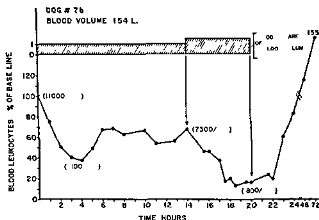
In preparation for surgical exploration of the right kidney region venesection daily for four days reduced hematocrit to 43 hemoglobin to 13 6 Gm and erythrocytes to 4 500 000 with remarkable subjective improvement At operation in January 1950 an encapsulated tumor about 9 cm in diameter was found at the lower pole and right nephrectomy was performed The right adrenal was normal and was left undisturbed

Symptoms and polycythemia disappeared after operation and did not recur *In June 1955 5½ years after operation she was married*

(5) Northwe t M d 54 976 979 S pt mber 1955

lets The buffy coat cells were counted after mixing More efficient removal of white cells occurred when blood mixed with dextran was centrifuged but reactions in some animals to this material discouraged its general use The animals received an injection of penicillin and streptomycin sometimes required supplemental transfusion of their own blood drawn one to two weeks before the experiment and were given supplemental calcium and magnesium to balance excess losses due to the chelating agent used In radiated dogs the dose was 250 r (LD) whole body irradiation

Of 17 dogs 15 became leukopenic (under 2 000 white blood



F g 68—F l f l k ph t d l k p u t l t f lea l t d N t d l y n y f blood l kocyt ft p l g d t ou l k ph (Court y f C ddock C G J t l J Lab & Cl M d 45 881 905 J 1955)

cells/cu mm) in a few hours Leukopheresis over a single day (Fig 68) caused leukopenia in all dogs and clearance of 1 5 blood volumes or more/hour for three hours was always effective During leukopenia epinephrine did not cause leukocytosis Counts done from femoral vein vena cava aorta brachial vein and skin of ear showed close agreement Direct microscopic inspection of the omental circulation in one animal showed very few leukocytes The white counts returned to 100% normal in about 4½ hours but did not start to rise for 30 90 minutes after leukopheresis was stopped This was true whether depletion was stopped promptly or as long

swelling for one month. Paracentesis for ascites yielded 2 000 cc amber fluid An abdominal mass was thought to be the liver or an upper abdominal tumor Hemoglobin content was 20 7 Gm /100 ml color index 0 99 and erythrocyte count 7 000 000/cu mm Leukocytes numbered 16 000/cu mm with 83% neutrophils 14% lymphocytes and 3% monocytes Bromsulfalein retention was 72% after 45 minutes thymol turbidity 1 3 Maclagan units total serum protein 6 8 Gm /100 ml —4 7 Gm albumin and 2 1 Gm globulin Ascitic fluid smear revealed clusters of abnormal cells believed to be tumor cells Diagnosis after exploratory laparotomy was hepatomegaly and splenomegaly with portal hypertension secondary ascites and chronic cholecystitis with cholelithiasis She died in shock about 15 hours after operation Principal autopsy findings were enlarged liver (2 100 Gm) and spleen (550 Gm) Sections through the liver showed old gray white firm thrombi completely plugging lumens of two major tributaries to the hepatic vein One vein in the right lobe contained a recent thrombus surrounded by parenchymal necrosis Numerous small tributaries of the hepatic vein also were thrombosed There was no malignant change or enlarged nodes Anatomic diagnosis was Chiari s syndrome secondary to or associated with polycythemia vera Although symptoms in this patient were of short duration microscopic findings suggested that pathologic change had begun considerably earlier hence the case probably should be classified as chronic

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LEUKOCYTOSIS AND LEUKOPENIA

Studies of Leukopoiesis Technic of Leukopheresis and Response of Myeloid Tissue in Normal and Irradiated Dogs are described by Charles G Craddock Jr William S Adams Seymour Perry William A Skoog and John S Lawrence[7] (Los Angeles)

Method.—Healthy mongrel dogs were subjected to cannulation of the femoral artery and vein with a siliconed glass cannula or polyethylene tubing Base line cell counts were made repeatedly for one hour on arterial blood. Blood volume was measured by Evans blue method. Blood removed in 40 50 ml aliquots was placed in plastic centrifuge tubes containing 0 3 ml 10% ethylenediamine tetra acetate disodium and centrifuged 15 minutes at 2 800 rpm The plasma was separated from the buffy coat the buffy coat removed en masse along with the upper layer of red cells and platelets and the plasma and red cells reconstituted for readministration to the animal Counts made on such blood showed 85 90% removal of white cells and plate

(7) J Lab. & Clin Med 45 881 905 June 1955

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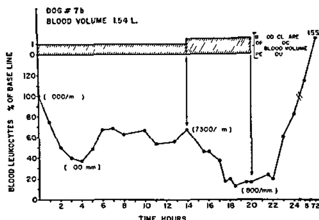


Fig 68 —F l f l k ph t d leuk p u t l rat f l w ce l t f Not d lay n ry f blood t kocyt ft p l ged cont l koph (Courte f C ddock C G J t l J Lab & Cl M d 4 881 905 J 1955)

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(7) J Lab. & Clin Med. 45 881 905 June 1955

• [These observations are basic to our understanding of the physiologic control of leukocyte levels —Ed]

Effect of Chloramphenicol and Other Antibiotics on Leukocyte Respiration. A growing number of reports have indicated that antibiotics may cause severe blood dyscrasias in susceptible individuals In general penicillin streptomycin chlortetracycline and oxytetracycline appear to be relatively nontoxic to blood forming organs Chloramphenicol has been more seriously implicated Since 1951 numerous reports have shown that its prolonged or repeated use may result in severe leukopenia agranulocytosis thrombocytopenia and aplastic anemia in certain individuals although toxic effects have been sporadic and have occurred in only a small proportion of persons receiving the antibiotic In an effort to elucidate the basic mechanism involved James H Follette Peter M Shugarman John Reynolds William N Valentine and John S Lawrence[8] (Univ of California Los Angeles) studied the effect of these antibiotics and of atabrine® and urethane on the respiratory metabolism of separated leukocytes

Chlortetracycline oxytetracycline penicillin and streptomycin have little or no effect on leukocyte respiratory activity but chloramphenicol produced significant inhibition when used in the same concentration Moderate inhibition of oxygen uptake occurs with chloramphenicol at concentrations of 1×10^{-3}M this increases progressively until almost complete inhibition at $6\,1 \times 10^{-3}$ M Inhibitory activity of chloramphenicol is intermediate between that with atabrine® and with urethane

The concentrations used exceed those usually found in the serum of patients receiving these compounds by mouth whether hematopoietic tissues would be exposed to drug levels of equal magnitude in vivo is not known The possibility exists however that selective concentration may occur e g in bone marrow The demonstration that chloramphenicol suppresses oxygen consumption of leukocyte homogenates in vitro cannot be assumed to represent a mechanism for hemopoietic depression in vivo it merely delineates a pharmacologic activity The toxic effect of chloramphenicol

(8) Blood 11 34 4 M h 1956

as six hours after maximal leukopenia was achieved Differential cell counts showed a mild shift to the left during recovery with a few myelocytic forms appearing after 24 hours Lymphocytes practically disappeared during leukopheresis and remained low during recovery If leukopheresis was repeated on three successive days recovery from leukopenia was successively more rapid Not only did replenishment of leukocytes begin promptly on (or before) cessation of leukopheresis but there followed marked leukocytosis In only one animal did the imposed demand appear to exceed the supply of leukocytes

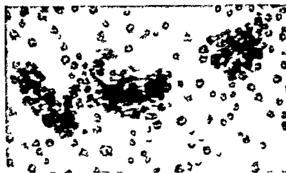
Marrow studies showed immaturity of the myeloid series appearing by the third day the maximum on the fourth or fifth day with marked myeloid predominance

Irradiation of the animals one hour before leukopheresis resulted in a prolonged delay before leukocyte levels began to rise The rise was steady reaching a maximum in 24 hours A second depletion induced leukopenia gradually and only after persistent depletion On cessation however leukocytosis appeared promptly but did not achieve the initial height seen after the first episode After a third leukopheresis considerable numbers of myeloid cells were found in fecal discharge There was a slowly progressive fall in white blood cells reaching extreme depths nine hours later One of three animals lived to recover from this event Marrow and peripheral blood showed no immaturity of cells only successively fewer cells The surviving dog showed prolonged leukopenia until two weeks after hyperplasia of marrow occurred

The authors concluded that the removal of leukocytes from the circulation results first in release of leukocytes from storage areas and later in acceleration of growth processes Both normal and irradiated dogs can rapidly replace the number of leukocytes circulating in the peripheral blood many times although the irradiated dog shows delayed replenishment and becomes unable to respond with leukocytosis if repeatedly depleted Ability to develop leukocytosis depends on adequate stores of cells that can be rapidly released into the circulation whereas ability to respond to repeated depletions depends on acceleration of production of myeloid cells

hyperplastic in the myeloid series No tumor cells were seen Despite antibiotics cortisone and testosterone she contracted fungal and bacterial pharyngitis with later pneumonia and died Aside from the ulcerative and inflammatory lesions of esophagus and lung autopsy revealed a normal liver congested spleen and purple bone marrow White blood cell elements of the marrow showed a left shift with scattered plasma cells the over all picture being that of myeloid maturation arrest No neoplastic tissue was found and diagnosis was agranulocytic angina

TECHNIC—Fresh serums serums stored at −15 C and serums



F g 69—St gly p t l k gglut n t D wh t blood ll b t d w h rum f p t t (Cou t y f S hw t R S d H W K. A M 4 A h I t M d 95 863 868 J e 1955)

stored at 4 C for one to three days were used Before incubation serum was heated to 56 C for 30 minutes to allow maximal agglutination Over 20 serums from patients with various diseases failed to show leukoagglutinins The positive control was an antileukocytic rabbit serum To prepare white blood cell suspensions 25 ml blood was defibrinated in a flask with 10 glass balls and the blood decanted To this blood 1/5 volume high molecular weight dextran was added and the mixture allowed to settle in a 37 C water bath The supernate was pipetted off and stored at 4 C for short periods before use Donor cells so prepared were taken from numerous compatible bloods To 0 2 ml test serum 0 1 ml white blood cell suspension was added the mixture incubated at 37 C one hour and the tubes then agitated five minutes Two drops of 2% acetic acid were added and a drop of the mixture was placed on a glass slide and examined microscopically A negative test result showed uniform dispersion of cells in all fields Positive test results (Fig 69) were graded +1 to +4 on basis of size and number of white blood cell aggregates Agglutination was not inhibited by use of siliconized glassware Sterile technic did not

toward hemopoietic tissues is most likely due to its nitrobenzene radical Nitrobenzene by itself is known to produce methemoglobinemia in susceptible individuals and may paradoxically result in polycythemia [This is because the oxygen capacity of the arterial blood is reduced by the presence of methemoglobin with resulting stimulation of erythropoiesis —Ed]

The authors experiments have so far failed to indicate a relation between flavin dependent enzymes and observed inhibition of respiration by chloramphenicol Cytochrome oxidase likewise does not appear to be a site of action Further studies will be necessary to elucidate whether the metabolism of Krebs cycle intermediates in the leukocyte and also whether entry of active metabolites such as pyruvate or active acetate into the tricarboxylic acid cycle are affected by chloramphenicol

• [It is of interest that Erslev and others have shown that in patients developing progressive anemia while receiving chloramphenicol discontinuance of the drug may be followed promptly by increased erythropoiesis —Ed]

Leukoagglutinins in Agranulocytosis Report of Case is presented by Robert S Schwartz and William K Hass[9] (Montefiore Hosp New York) An immunologic mechanism has long been suspected as a key factor in the pathogenesis of certain types of agranulocytosis and in syndromes characterized by paucity of erythrocytes or platelets In the last few years coating antibodies have been discovered in acquired hemolytic anemia and platelet agglutinins have been demonstrated in idiopathic thrombocytopenic purpura The present case is the first reported with autopsy findings Cause of agranulocytosis was unknown

Woman 55 with radical mastectomy for anaplastic carcinoma had axillary metastases treated postoperatively with 1 800 r radiotherapy for a month when treatment was stopped because white blood cell count was 2 400/cu mm Hypoplastic marrow was found Results of examination were normal except for effects of operation Direct and indirect Coombs tests were normal Epinephrine caused no leukocytosis A leukoagglutinin was repeatedly demonstrated Paper electrophoresis was normal except for an alpha peak X rays showed no metastases The bone marrow specimen first showed normal myeloid erythroid ratio but leukocyte population was 50% blast forms Later early myelocytes predominated while another specimen was

(9) A M A Arch I t M d 95 863 868 J 1955

influences on certain leukocytic activities and functions (table) In all 350 histochemical procedures were carried out on peripheral blood and bone marrow smears and imprints or smears from spleens and lymph nodes in many instances biochemical determinations were made on separated leukocytes of these patients

In normal subjects most of the polymorphonuclear leukocytes showed no alkaline phosphatase about 20 40% of cells revealed a ± 2+ staining intensity An average of 21 9 mg of P was liberated per hour by 10^{10} leukocytes with a range of 18 26 mg In all pyogenic infections leukocytes showed greatly increased alkaline phosphatase activity In one case of Weil s disease and in several of pulmonary tuberculosis enzyme activity was also markedly elevated In three cases of infectious mononucleosis alkaline phosphatase activity was negligible in neutrophils of peripheral blood Neutrophil leukemoid reactions may be seen in various clinical disorders such as myeloid metaplasia carcinoma and hepatic cirrhosis Since these disorders may simulate chronic myelogenous leukemia closely determinations of high cellular alkaline phosphatase activity in polymorphonuclear leukocytes in these conditions are of practical diagnostic aid

In acute leukemia immature neutrophilic leukocytes are devoid of alkaline phosphatase In chronic myelogenous leukemia this enzyme is seen only as a faint ± stain in an occasional cell An average of 7 8 mg of P was liberated per hour by 10^{10} white blood cells In 9 multiple myeloma and 10 chronic lymphatic leukemia cases alkaline phosphatase appeared normal by biochemical technic but histochemical method showed intense staining of almost every adult neutrophil By correlation of biochemical readings to 10^{10} segmented and band form neutrophils it became obvious that in these diseases unit cell alkaline phosphatase activity was greatly elevated

The function of alkaline phosphatase in the neutrophil is unknown it has been postulated that it may play a role in reaction to infection or other stress phenomena Another possibility is that it participates in intrinsic metabolic activity of the cell The authors suggest that the neutrophil may be a vehicle for transport of this enzyme from bone

alter results Heparin caused unreadable microscopic fields Sapon lysed the red blood cells but caused clumping in all tubes

Histochemical and Biochemical Studies on Leukocyte Alkaline Phosphatase Activity have demonstrated marked differences in enzyme activity in cells that appear morphologically similar E Wiltshaw and W C Moloney[1] (Boston City Hosp) report initial investigations in 150 patients using these procedures in evaluation of physiologic and patholog

SUMMARY OF CASES AND MATERIAL STUDIED FOR ALKALINE PHOSPHATASE BY HISTOCHEMICAL TECHNIC

		NO CASES	NO. P BL	NO BONE MARROW	NO SPLEENS	NO NODES
NORMAL		14	31			
ACUTE LEUKEMIA		9	12	9	1	1
CHRONIC LEUKEMIA	MYELOGENOUS	7	38	2	1	
	LYMPHOCYTIC	10	27	3	1	2
MYELOID METAPLASIA		4	8	1	1	
POLYCYTHEMIA VERA		1	2			
LEUKEMOID REACTIONS	INFECTION (PYOGENIC)	[illegible]	21	4		
	MALIGNANCY	6	5	2		1
	CIRRHOSIS	12	13	8		
	INFECT MONO	3	5			
	TUBERCULOSIS	7	6	1		
	OTHER INFECTIONS	5	3	3		
MULTIPLE MYELOMA		9	15	10		
HODGKINS DISEASE AND LYMPHOMATA		12	25	4		
PERNICIOUS ANEMIA AND FOLIC ACID DEFICIENCY		7	8	6		
MISCELLANEOUS CONDITIONS		39	37	27	4	2
TOTAL NUMBERS		1_0	2 6	80	8	5

(1) Blood 10 1120 1131 November 1955

primary exposure to typhoid paratyphoid antigens and four days after a later secondary exposure to the same antigens Similarly in normal children (controls) lymph nodes were obtained before antigenic stimulation in four instances after primary antigenic stimulation with typhoid paratyphoid antigens in five instances and during the secondary response in four instances

The marrow of patients with agammaglobulinemia was grossly deficient in plasma cells Virtual absence of plasma cells in the marrows of three of the patients and extreme reduction of their numbers in a fourth permit a qualitative separation of the marrows of these patients from those of normal persons or persons with other diseases Stimulation with typhoid paratyphoid antigens in each of the normal children resulted in significant plasmacytosis associated with marked increase in agglutinin titer whereas patients with agammaglobulinemia failed to produce antibodies and plasma cells in the bone marrow Except for plasma cells all cell types seen in the lymph nodes of normal children were found in the nodes of patients with agammaglobulinemia Small numbers of plasma cells were regularly found in the nodes of normal children Following antigenic stimulation hypertrophy of the lymph nodes occurred in both normal children and patients with agammaglobulinemia Whereas in the nodes of normal children the number of plasma cells increased in those of children with agammaglobulinemia no plasma cells or secondary follicle formation was noted

These observations suggest that plasma cells are directly involved in formation of antibodies and gamma globulin and liberation of these proteins into the circulating blood and that they produce circulating antibody in man Thus study of functions and requirements of plasma cells may be an incisive approach toward understanding and ultimate control of the immune response

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LEUKEMIA AND RELATED DISORDERS

Production of Leukemia by Filtrable Agent from Malignant Tumors The work of Gross (1950-55) has altered the direction of research on the etiology and pathogenesis of

marrow to other sites hence attempts were made to study relative concentration of alkaline phosphatase in leukocytes of peripheral blood and bone marrow drawn simultaneously Although all possibility of errors cannot be excluded it appears that histochemically and biochemically there is no consistent difference between these materials When leukocytes were incubated in their own serum the enzyme activity doubled itself in about two hours and rose gradually to reach equilibrium between four and six hours When white blood cell suspensions from normal persons and patients with chronic myelogenous leukemia myeloid metaplasia and pyogenic infections were incubated in saline and various serum cell alkaline phosphatase rose during incubation independently of the serum or saline menstruum

Studies on Agammaglobulinemia II Failure of Plasma Cell Formation in Bone Marrow and Lymph Nodes of Patients with Agammaglobulinemia. There is evidence for extrahepatic antibody and gamma globulin formation Lymph nodes spleen and bone marrow have been found to produce antibodies and experiments have suggested that plasma cells are one of the cellular sources of antibody production in experimental animals Some authors still doubt this relation or advocate different cells as the source of humoral antibody and gamma globulin

Robert A Good (Univ of Minnesota) sought evidence for the cellular basis of antibody and gamma globulin formation in patients who could form neither antibodies nor gamma globulin He found that both children and adults with agammaglobulinemia showed striking deficiency in numbers of plasma cells in the hematopoietic tissues

Good studied two boys aged 7 with congenital agammaglobulinemia and two adults with the acquired illness Studies revealed that both children showed almost complete paralysis of the immunologic mechanism Even the so called natural isohemagglutinins were lacking from the circulation and could not be demonstrated after challenging injections of large volumes of washed red blood cells of heterologous blood groups

Lymph nodes were obtained from the agammaglobulinemic patients before antigenic stimulation four days after

(2) J Lab & Cl Med 46 167 181 August 1955

oncogenic virus type agents In the authors experiments with the SOV 16 tumor a similar change in specificity was observed within a relatively short time histologic and general appearance of a generalized leukemia shifted in the direction of a tumor like leukosis with sarcomatous appearance and preferential localization in the thymus

Characteristics of a Virus Isolated from Hodgkin s Disease Lymph Nodes It has long been suspected that an infectious agent may be a factor in Hodgkin s disease but it is now apparent that bacteria have no direct relation The serial passage of ground Hodgkin s disease lymph node material in chicken eggs and the effect of these bacterially sterile lymph node extracts on the growth of known viruses have suggested that certain virus like characteristics could be demonstrated Extensive experiments with inoculation of Hodgkin s disease material into adult animals have demonstrated that no discernible disease was induced Warren L Bostick and Lavelle Hanna[4] (Univ of California) report a technic and the results of a new approach by studying the effect of Hodgkin s disease material in young animals

Hodgkin s disease and control human lymph node tissues were compared by intracerebral serial inoculations into suckling mice After five to seven blind passages a viral agent was detected in three cases of Hodgkin s disease two of which have been maintained and studied Although the same mouse strain and technics were used in the control material no agent was encountered

Viruses isolated from Hodgkin s disease tissues produced a *fatal encephalitis manifest 7 10 days after inoculation* Only intracerebral injections were effective in the initially isolated strain After 17 serial intracerebral passages in mice the strain became adapted to intraperitoneal transfer

Microscopically the lesion was a diffuse severe encephalitis demonstrating chiefly a round cell response The spinal cord was also affected diffusely so that the clinical symptoms were ataxia flaccid paralysis and death Complete microscopic examination failed to reveal inflammation in muscles fat liver pancreas lungs kidneys etc

The agent was inactivated at 56 C in 30 minutes and was

(4) Ca Res 15 650 656 Novembe 1955

leukemias which are generally regarded as malignant tumors of blood forming organs He demonstrated in convincing and basic experiments that leukemia of inbred AK mice could be transmitted by means of a cell free filtrate to unaffected newborn mice of the C3H strain This showed that leukemia of AK mice is produced by a virus like agent and raised the question whether this might be the etiologic mechanism in all leukemias or even more generally in all types of malignant tumor

A Graffi H Bielka and F Fey[3] (Berlin) have reported numerous studies with filtrates from various tumors and here summarize results pertaining to leukemias Filtrates were prepared from malignant mouse tumors Sa I and Sa II SOV 16 and ascites carcinoma by mincing and homogenizing the tissue which was then filtered twice and centrifuged at speeds of 3 500 18 000 rpm only the supernatant fluid was used These cell free filtrates were injected into newborn mice in which leukemia was produced 254 times i e in 34-75% of surviving animals (range for the four types of tumors) There were myeloid forms and also a high proportion of chloroleukemia

The method of preparing the filtrate definitely excluded the possibility that malignant cells might have participated in causing the leukemias A nonspecific effect was practically excluded by negative results obtained on heating the filtrates to 85 C and also by control experiments with normal homologous and heterologous tissues and tumors The most likely explanation of the results with cell free filtrates is that leukemia was caused by a virus like agent derived from the nonleukemic tumors

The chief point of difference from the observations reported by Gross is that in the present experiments leukemia was produced from solid nonleukemic tumors (sarcomas and carcinomas) and that myeloid and chloroleukemias—not lymphatic leukemias—were produced Gross however, noted other types of tumors after injection of filtrates of lymphatic leukemia tissues particularly bilateral tumors of the neck which he called salivary gland cancers This raises the question of variability and transient histiospecificity of

(3) Acta ha mat. 15 145 174 1956

to be of little value Leukoses in young infants are rather often associated with various anomalies especially cardiac malformations and mongolism The latter has been observed in three recently reported patients Some authors have pos tulated embryopathy as the cause of both the blood disease and the anomaly That such association may be encountered in leukoses which appear later in older children does not disprove this hypothesis because the period of incubation of leukosis is extremely variable in different persons The pe riod of fetal life during which these various malformations are established (mongolism interventricular communica tion dextrocardia radial aplasia etc) is between the 5th and 14th week and it is known that granulopoiesis does not ap pear until after the 4th month This does not contradict the embryopathic hypothesis because at this fetal period hema topoietic tissue capable of transmitting the leukemogenic factor exists as has been demonstrated in spontaneous leu koses in certain animal strains

Acute Nonlipid Disseminated Reticuloendotheliosis Ran dolph Batson John Shapiro Amos Christie and H D Riley Jr[6] (Vanderbilt Univ) add 15 cases to the 41 in the litera ture and present data which support the concept that dissem inated reticuloendotheliosis (Letterer Siwe disease) is but an infantile usually fatal form of a disease spectrum which in other age groups extends through Hand Schuller Chris tian disease to eosinophilic granuloma The manifestations depend only on the subject s age and the chance distribution of lesions This view accounts for the numerous transitional cases reported in the past and reviewed by the authors

The patients were between 1 and 13 months of age at onset of the disease and demonstrated variously hepatosplenomeg aly anemia skin lesions adenopathy bone lesions and re curring secondary infections With one exception all diag noses were confirmed pathologically The younger patients survived only a few weeks the older patients for months Secondary infections often obscured the primary disease in the younger infants Purulent otorrhea was present in over half and two had mastoiditis other secondary infections in cluded pharyngitis purulent rhinitis gastroenteritis impeti

(6) A M A Am J D Ch ld 90 3 3 343 S ptembe 1955

resistant to ether It produced no discernible lesions in chicken eggs or in tissue culture Complement fixing anti bodies could be produced in immunized rabbits and with difficulty in young adult mice No neutralizing antibodies have been produced in these animals Human Hodgkin s dis ease and control serums have not been found to possess complement fixing antibodies Commercial human immune globulin possessed neutralizing ability

Effort has been made to rule out the possibility that the isolated agents may represent examples of latent mouse or chicken virus The agent is believed to be a new type of virus which has truly been isolated from human Hodgkin s disease lymph node tissues The direct relationship of this virus to Hodgkin s disease must be clarified by further research

Leukoses of Very Young Infants (Leukoses of Newborn Leukoses of First Six Months of Life and Leukoses Associ ated with Congenital Malformations Jean Bernard G Mathe J Cl Delorme and O Barnoud[5] (Paris) report 10 cases and review 80 previously reported The main symp toms of leukoses of the newborn of which the authors ob served one case are hemorrhages splenomegaly and fever Anemia is not always present osseous manifestations and adenopathies are rare and cutaneous localization frequent In the nursing infant principal signs of leukosis are anemia and splenomegaly often but not constantly fever and hem orrhage Adenopathies are late Cutaneous lesions are fairly frequent, but so far bone involvement has not been de scribed

Leukopenic conditions are unknown in the newborn and are very rare in nurslings In both leukocytosis is often in creased and is nearly always accompanied by circulation of abnormal leukocytes in the blood The leukemic picture is inconstant The diarchic type proliferation not seen in the newborn is not infrequently encountered in the young in fant The myelogram sometimes shows a monomorphic leu koblastosis sometimes a polymorphic picture similar to that of myeloid leukemia in the adult

The course of infantile leukosis is usually very short An tileukemic treatment has rarely been administered and seems

(5) Arch franç pédiat 1 470 50 1955

had lost a sibling with a similar disease who was not exam ined pathologically Two patients with characteristic clinical pictures and biopsies appeared to recover from the disease possibly due to antibiotic therapy

Final confirmation of the diagnosis rests on the character istic microscopic picture even though gross autopsy find ings usually suggest the basic disease Focal aggregations of pleomorphic large mononuclear cells constitute the unit lesions but almost always with an admixture of plasma cells



Fg 71—Lymph nod w th ma filt t on b b t ocy ll (x) A w d t m g lymph d t (Cou t y f B tso R et l A M A Am J D Ch ld 90 3 3 343 S p mbe 19 5)

and lymphocytes and frequently with eosinophils and neu trophils in appreciable numbers In a single lymph node (Fig 71) variation may occur between proliferation of im mature mononuclear cells and obliteration of normal archi tecture to the extent that reticulum cell sarcoma is sug gested whereas other areas of abundant large mature mononuclear cells are seen with phagocytosed debris in their cytoplasm Nodular or diffuse infiltrations of large mono nuclear cells may occur in unusual locations as in the sub arachnoid space pancreas ureter gallbladder adrenal and submucosa of the gastrointestinal tract at times suggesting

go scalp abscess meningitis pneumonia and thrush Pulmonary infiltration present in x rays of several patients was present pathologically in all so studied The characteristic maculopapular rash (Fig 70) was not confined to younger infants and usually appeared first in the scalp and hairline later becoming generalized but more pronounced in skin folds The lesions were elevated with a greasy appearing scaly surface Hemorrhage was pronounced in some of the skin lesions but hemorrhagic lesions occurred in absence of rash Generalized adenopathy was present in 10 patients and was more marked in the older infants with a longer course as was hepatosplenomegaly which was never massive Bone lesions (five patients) were more common in older infants Under x ray observation many lesions healed even while new osteolytic lesions were appearing or becoming more extensive Pathologically proliferative and healed lesions osseous and visceral could be seen simultaneously in the same patient Lowered platelet counts and hemoglobin levels were attributed to reticuloendothelial proliferation or hypoplasia of the bone marrow Total serum proteins were usually low but not consistently



Fig 70 —Characteristic rash in acute nonlipid disseminated reticuloendotheliosis (Courtesy of Batson R et al J A M A Am J Dis Child 90 323 343 September 1955)

Disseminated histoplasmosis can produce a similar clinical picture except for the rash and bone lesions However in all cases diagnosed pathologically Histoplasma capsulatum has always been easily cultured whereas in acute disseminated reticuloendotheliosis this organism was never cultured despite special efforts Other attempts to isolate or identify a specific infective agent by cultural and immunological means were unsuccessful Two patients were siblings and another

curred in 13 and perirectal lesions in 5 In one anal fi sure disappeared after remission of the disease with 6 mercapto purine treatment but reappeared five months later during relapse Skin lesions were present in only two Lymphade nopathy was generally slight and hepatosplenomegaly mod erate Most patients had moderate leukocytosis when first seen but several had normal white cell counts Invariably unless depressed by therapy white cell count rose terminal ly to over 100 000 Three patients with initial white cell count of over 100 000 died within three weeks five weeks after on set of symptoms Many nucleated red cells were often found in the blood smear Bone marrow was uniformly densely cellular mostly with blast cells promonocytes and a few mature monocytes Megakaryocytes were reduced as were normal myeloid and erythroid cells These patients had an acute rapid course One patient lived six months but death usually occurred within two months Specific antileukemia therapy in four patients seemed to prolong life a few months longest survival was 8½ months

The literature revealed only 14 cases fulfilling the authors criteria for chronic monocytic leukemia The authors add eight cases of their own Ages ranged from 17 to 76 but only 3 of the 22 were under 40 16 were men These cases did not conform to any specific pattern The most common type had an initial preleukemic phase characterized by anemia and other cytopenias with cellular nonleukemic bone mar row During this phase these cases clinically resembled aplastic anemia but there were slowly progressive changes which finally culminated in obvious leukemia Anemia was present at initial examination in every patient it was usually normocytic and normochromic but in some instances was macrocytic In most cases leukopenia was ob erved early and tended to persist throughout most of the illness Granulocy tosis in response to infection did not occur even when blood was not leukemic and myeloid cells were plentiful in the mar row In most of these cases leukocytosis and monocytosis typical of acute leukemia were noted during the terminal period In a few leukopenia persisted until death In only a few was there appreciable absolute monocytosis over an ex tended period

tumorous deposits similar to those occasionally seen in leukemia Small foci of coagulative necrosis with collections of polymorphonuclear leukocytes may be seen in association with *massive infiltration of immature large mononuclear* cells Fibrous tissue proliferation may suggest the healing of an inflammatory process In addition to these large cells with lobate nuclei may resemble Reed Sternberg cells closely and suggest Hodgkin s disease

Skin lesions, when fully developed are highly characteristic and consist of focal accumulations of atypical mononuclear cells confined to the corium and often in relation to a kin adnexal gland Lymphoid tissue shows characteristic atrophy of normal elements and variable degrees of cellular proliferation In the bone marrow atypical mononuclear cells may be present in large numbers or only sparsely Infiltration into the lungs liver and kidneys was so frequent as to be considered almost specific In the lungs the submucosa of the bronchi and adventitia of the vessels as well as the alveolar septa exhibited variable degrees of large mononuclear cell infiltrate not seen in this localization in other disease states In the liver a unique infiltration of cells occurred in the portal areas Plasma cells and lymphocytes were present as well as large mononuclear cells and occasionally this infiltration was grossly visible Variable degrees of fibrosis and bile duct distortion occurred and in two cases with intralobular bile stasis there was sufficient fibrosis to be classified as cirrhosis The kidney showed focal cortical accumulations of large mononuclear cells with some plasma cells and lymphocytes These lesions occurred in the periglomerular interstitial tissue with no change in the glomeruli

• [Satisfactory clinical and pathologic descriptions of this rare disorder are not frequent in the literature It is interesting that skin lesions which are prominent in chronic monocytic (or histiocytic) leukemia in adults are here also associated with dermal infiltrations of large pleomorphic mononuclear cells —Ed.]

Monocytic Leukemia is summarized in 17 cases and a review of the literature is made by Charles M Sinn and Frederick W Dick [7] Ages of 17 patients with acute monocytic leukemia observed at Johns Hopkins Hospital ranged from 16 to 83 with a mean of 53 Lesions of the oral cavity oc

(7) Am J Med 20 585 602 Ap 1 1956

Following therapy with cortisone 6-mercaptopurine or amethopterin urinary excretion of uric acid increased in acute leukemia as the leukocyte count declined As the leukocyte count approached normal levels uric acid excretion decreased Urinary excretion of xanthine and guanine paralleled excretion of uric acid Administration of an aromatic nitrogen mustard derivative to one patient with chronic lymphocytic leukemia and of dimethanesulfonyloxybutane (myleran) to one with chronic myelocytic leukemia was accompanied by only slight increase in uric acid excretion

Excretion of large amounts of uric acid following antileukemic therapy can be explained by at least two hypotheses (1) Destruction of cells already in the circulation marrow and tissues with rapid breakdown of nucleic acids and increased excretion of uric acid (2) Inhibition of production of leukemic cells by interfering with reutilization of catabolites of nucleic acids derived from white blood cells or by interrupting formation of new nucleic acids

Additional study is necessary to decide whether uric acid excretion is a rough measure of rate of turnover of leukocytes Recent studies suggest that the life span of most lymphocytes in chronic lymphocytic leukemia is considerably longer (80 300 days) than that of myeloid leukocytes (12 days) This is compatible with the normal uric acid excretion in chronic lymphocytic leukemia demonstrated by the authors

Determination of Weight and Volume of Liver Cells in Leukemia Robert L Wolf and Paul Klemperer[9] (Mount Sinai Hosp New York) studied livers from 13 patients without hepatic disease and enlarged livers from 9 patients who died of acute subacute or chronic myelogenous leukemia or chronic lymphogenous leukemia Number of hepatic cells was determined by a counting chamber technic and weight and volume of hepatic cells were determined as ratios to gross weight and volume

Both weight and volume per liver cell are greater in livers from patients with leukemia than in normal livers Quantity of leukemic cells was not sufficient to explain increase in

(9) Am J Cl P th 25 988 993 S pt mbe 1955

Splenectomy was peformed in six patients bec u e of ane mia neutropenia and sometimes thrombocytopenia with cellular bone marrow in two monocytic infiltrations in the spleen led to the correct diagnosis but in four the spleen was histologically normal The rarest type of chronic monocytic leukemia is that in which monocytosis of considerable degree consisting of mature cells, is present in the blood for a long time

The relation of preleukemic forms of monocytic leukemia to aplastic anemia seems to be more than chance It is suggested that toxic stimuli may cause hyperplasia with interference in normal maturation and release of marrow cell hyperplasia of marrow with prominence of more primitive reticuloendothelial cells or complete hypoplasia of marrow In preleukemic cases neoplastic change eventually occurs and becomes manifest clinically These cases may represent one continuous disease process In experimentally induced leukemia in animals there is no sudden irreversible cellular change but rather a train of events in which irreversible change may occur

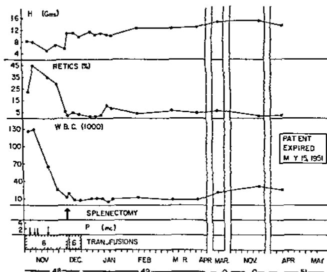
• [It is our impression also that chronic monocytic leukemia in the adult may appear as peripheral pancytopenia without clear evidence of leukemia in the bone marrow or blood over a period of months —Ed.]

Studies on Leukemia I Uric Acid Excretion Since 1870 it has been known and often confirmed that uric acid excretion may be increased in some patients with leukemia but this is not a consistent finding Whether uric acid excretion correlates with morphologic type of leukemia degree of elevation of leukocyte count or degree of enlargement of spleen or other tissues is not known and influence of modern chemotherapeutic agents on uric acid excretion has not been studied For these reasons A A Sandberg G E Cartwright and M M Wintrobe[8] (Univ of Utah) studied urinary excretion of uric acid in 38 patients with various types of leukemia

Mean excretion of uric acid in 17 normal subjects was 6 5 mg /kg /24 hours in 14 patients with acute lymphoblastic leukemia it was 30 3 mg in 13 with acute myeloblastic leukemia 13 0 mg in 6 with chronic lymphocytic leukemia 5 2 mg and in 5 with chronic myelocytic leukemia 13 5 mg

(8) Blood 9 154 166 February 1956

One patient with splenic granulocytopenia with clinical manifestations of agranulocytosis responded dramatically to splenectomy One patient thought to have splenic thrombo cytopenia died one month postoperatively without showing any improvement in platelet level or bleeding manifesta tions Of five patients with mixed types of dyssplenism two



F g 72—Labor t ry d th py dat w man 73 w th h on lymphocyt c l k m d econd y q d h m lyti tn th t pond d to pl ect my (L rt y f R nh d E H d Loeb V J J A M A 158 6 9 634 J e 25 1955)

showed an excellent response to splenectomy with an in crease in all involved cellular elements two showed moder ate improvement and one received no benefit The three pa tients with Hodgkin s disease showed marked improvement after operation of brief duration in one The patient with reticulum cell sarcoma died one month after splenectomy—insufficient time for evaluation Although patients who bene fit from splenectomy are often those helped by cortisone several in this series were not improved by cortisone though significantly improved after splenectomy

The finding of nucleated red blood cells in the bone mar

weight and volume There was no comparable increase in renal weight in the same patients though a corresponding quantity of leukemic cells was found in renal capillaries Proportion of intact cells to isolated cell nuclei was identical in normal and leukemic livers

Possible explanations of increase in ratios include increase in weight and volume (1) of extracellular material (2) of hepatic cells or (3) of both extracellular material and hepatic cells Sections of livers from patients with leukemia stained with hematoxylin and eosin disclosed no alteration or increase of extracellular material and no significant degree of hepatic edema and hepatic reticular fibers were not thickened or increased There were no significant hepatic lesions Hence it is concluded that increase in ratios in livers of patients with leukemia is due to increase in weight and volume of individual hepatic cells Similar results were obtained by another investigator using microscopic measurements of tissue components of leukemic livers

Increase in weight of leukemic livers cannot be explained by the slight amount of iron seen microscopically Enlargement of the liver in leukemic patients appears to be due to increase in weight and volume of individual liver cells and not to increase in total number of liver cells

Dyssplenism Secondary to Chronic Leukemia or Malignant Lymphoma Edward H Reinhard and Virgil Loeb Jr[1] (Washington Univ) point out that it is important not to overlook dyssplenism as a possible factor in cytopenia of one or more of the formed blood elements in patients with chronic leukemia or lymphoma

Observations were made on 21 patients with dyssplenism who underwent splenectomy 17 with chronic lymphocytic leukemia 3 with Hodgkin s disease and 1 with a reticulum cell sarcoma Of 10 patients with chronic lymphocytic leukemia and hemolytic anemia alone 5 showed an excellent response to splenectomy manifested by gain in hemoglobin accompanied by decline of the elevated reticulocyte level (Fig 72) 1 showed moderate improvement and 4 either failed to respond or died shortly after operation The five patients either required no transfusions or a greatly reduced number

(1) J A M A 158 6 9634 June 25 1955

marrow showing little or no differentiation beyond the lymphoblast or myeloblast stage the concentrations were within normal range The mean concentration in patients with acute or subacute leukemia accompanied by some granulocytic differentiation in bone marrow was greater than normal but in some individuals the concentrations were normal Normal concentrations were found in patients with lymphocytic leukemia stem cell leukemia and myeloma

Abnormally high serum B_1 concentrations diminished when the intensity of the granulocytic proliferation was reduced—e g in patients with chronic myelocytic leukemia by x radiation and in polycythemia vera by P^3 The B_1 in the serums of these leukemic patients was nearly all in combined form and was associated with an increase in serum capacity for binding B_1 The B_1 concentration in leukocytes was low compared with the concentrations in other tissues Leukocytes however appear to contain material capable of binding B_1 The B_1 concentrations of tissues of a patient with chronic myelocytic leukemia who died in relapse were not increased The increased amount of B_1 in the serum may be derived from the breakdown of leukocytes or more likely from abnormally high retention in the serum of B_1 absorbed in the normal way from the intestine possibly due to the increased B_1 binding capacity of the blood

Studies in Leukemia III Agglutination of Human Leukemic Cells by Guinea Pig Serum is described by Steven O Schwartz Harold M Schoolman and Wilma Spurrier[3] (Cook County Hosp) Earlier they reported the presence in normal adult guinea pig serum of an agglutinin and precipitin against the cells and tissues of AKR lymphoma mice This serum reacts in a similar manner with human leukemia cells but not with human normal white cells In the present study the validity of this finding is explored and a relatively simple test described which will aid in differential diagnosis of leukemia especially in the leukopenic phase and of leukemoid reactions

TECHNIC —Oxalated blood is separated by centrifugation at 2,000 rpm until white cells form a distinct layer Buffy coat is pipetted off and washed twice with normal saline solution Cells are then sus

(3) J Lab & Clin Med 46 709 712 N embe 1955

row despite a decreased peripheral red cell count together with shortened erythrocyte survival time and increased fecal urobilinogen excretion was sufficient evidence to implicate dyssplenism in most cases Similarly, adequate megakaryocytes, peripheral thrombocytopenia demonstration of platelet agglutinins or occurrence of numerous myeloid cells in the bone marrow with granulocytopenia was suggestive of dyssplenism A satisfactory response to cortisone or corticotropin gave support to the concept of a splenic basis for cytopenia

At times splenectomy can be of significant value from a palliative standpoint in these cases, even though the patient has far advanced malignant disease

Serum Vitamin B_{12} Concentrations in Leukemia and Some Other Hematologic Conditions are reported by *D L Mollin and G I M Ross (Postgrad Med School London)* In earlier studies they found that total vitamin B_{12} concentration of serum (determined with Euglena gracilis var bacillaris as test organism) in 126 healthy normal subjects aged 15 70 ranged from 100 to 900 μμg /ml with a mean of 302 μμg with almost all the vitamin in combined form The mean serum B_{12} concentration in 190 patients with pernicious anemia in relapse was less than 100 μμg /ml in the majority it was under 50 μμg In patients with other blood disorders including acute and chronic leukemia serum B_{12} concentrations did not differ significantly from normal

The present study concerns 56 patients with leukemias of various types 32 with polycythemia rubra vera 8 with myelosclerosis 2 with leukemoid reactions 6 with myelomatosis 7 with aplastic anemia and 1 with chronic agranulocytosis Most patients were untreated at the time the assays were made

Mean serum vitamin B_{12} concentrations were above normal in chronic myelocytic leukemia (4 943) subacute myelocytic leukemia (980) polycythemia rubra in relapse (794) myelosclerosis (850) and chronic nonleukemic leukocytosis (1 265) The concentrations in all patients with chronic myelocytic leukemia were abnormally high ranging from 2 000 to 9 600 μμg /ml in patients with acute leukemia and with

(2) Brit J Hemat 1 155 172 Apr 1 1955

Among reasons for this rather surprising finding is the possibility that use of chemotherapeutic agents may fail to alter the course of acute leukemia in some instances while prolonging it in others the fact that of the series suitable for analysis from the literature only one was more recent than 1952 although publications to May 1954 were reviewed and finally that use of 6-mercaptopurine was not adequately represented in the survey

• [So far then in the therapy of acute leukemia chemotherapy has been of far greater theoretical interest than of practical value —Ed]

Management of Acute Leukemia in Adults is discussed by F G J Hayhoe and Lionel Whitby[5] (Univ of Cambridge) on the basis of 50 cases studied during five years

Blood transfusions in 41 patients were assessed before other therapy was used 14 showed significant improvement and 5 had remissions lasting two to six months Lymphoblastic leukemia is more likely to respond to transfusions than myeloblastic or monoblastic types

Ten patients were treated with cortisone uncombined with other radical therapy (initial dose 200 300 mg /day) without serious toxic manifestations Five remissions occurred three of them very good Two of the best remissions were in patients with lymphatic leukemia who had previously had complete temporary response to transfusion but had become refractory Cortisone induced remissions lasted from three weeks to over four months Cortisone and aminopterin given concurrently to two patients with lymphoblastic leukemia produced no response both died within eight days

In eight 6 mercaptopurine (6 MP) was used uncombined with other treatment generally beginning with 2 5 mg /kg daily and decreasing the dose or stopping treatment according to response Of five patients with myeloblastic leukemia one had good remission for two months one showed slight improvement followed by full remission with cortisone One with lymphoblastic leukemia failed to respond and one of two with monoblastic leukemia showed partial response for two months Moderate remission in monoblastic and a good remission in myeloblastic leukemia are of particular interest since these types are usually less amenable to therapy than the lymphocytic type Two of three patients treated with

(5) B J H mat 1 1 18 J y 1955

pended in saline in a concentration between 5 000 and 10 000 cells/cu mm To 0 05 cc of this suspension 0 1 cc of normal adult guinea pig serum is added the mixture is shaken well Tubes are incubated for one hour at 37 C read macroscopically and in each case checked microscopically

The white cells were studied in 433 patients 56 of whom had leukemia There were four false negative and three false positive reactions All the false positives appeared in patient with advanced tuberculosis Two of the false negative reactions were from patients extensively treated for chronic lymphocytic leukemia the other two from patients with obscure diseases in whom diagnosis of chronic granulocytic leukemia could never be proved during life but was established at autopsy Of various drugs employed in treatment only cortisone had effect on the results and this was inhibitory

This simple test appears to have value in diagnosis of aleukemic leukemias and in differentiating leukemoid reactions

• [If confirmed by others this represents an important diagnostic advance —Ed]

Influence of Chemotherapy on Survival in Acute Leukemia was analyzed by Arthur Haut Stanley J Altman G E Cartwright and M M Wintrobe[4] (Univ of Utah) in 103 cases observed personally and in 782 reported in the literature Longevity rather than remissions was used as an index of therapeutic effectiveness because remissions are not necessarily caused by treatment and even if they were death is not necessarily delayed as a result Septicemia or a cerebral vascular accident may cause death at a time when clinical and laboratory findings point toward remission and then longevity is not a full measure of influence of antileukemic agents Nevertheless these events occur more often in leukemic than in nonleukemic persons and bespeak failure of therapy thus supporting use of longevity as an index

Patients were divided into treated and untreated groups and separate analyses were made for several modes of therapy It was not possible to demonstrate that newer treatments (folic acid antagonists ACTH cortisone and 6-mercaptopurine) significantly increased total survival in these representative groups However in those who achieved at least one complete remission median survival had been increased from 4½ to 8 months a statistically significant difference

(4) Blood 10 875 895 September 1955

missions in 5 of 13 patients of various ages with acute leukemia and partial remissions in 2 others reported on by James R Fountain[6] (Leeds) Remissions however were only temporary and resistance to further therapy with 6 mercaptopurine (6 MP) eventually resulted Six of seven patients with chronic myeloid leukemia showed varying response One in the acute terminal phase had a remission lasting 4½ months Two patients with chronic lymphatic leukemia two with multiple myeloma and one with reticulosis of the skin did not respond whereas one with mycosis fungoides obtained some improvement

A delay of 7 28 days was usual before the drug took effect which suggests that four patients who died within the first week of treatment had received an inadequate trial In two cases a fall in leukocyte count with clinical improvement occurred within a few days of starting treatment One received a routine course the other with extremely acute myeloblastic leukemia with considerable hemorrhage was given an initial dose of 1 Gm in the first 24 hours with the hope that the drug s action would be more rapid Dramatic clinical and hematologic improvement followed within four days Although its value remains to be proved (another patient failed to respond rapidly to large doses) such a dosage scheme seems worth trying since in acute leukemia rapidity of action is of prime importance Both patients who responded rapidly to 6 MP had a high initial leukocyte count (over 100 000/cu mm) with primitive blast cells predominant Whether patients who experience a complete remission should receive a daily maintenance dose remains to be answered though it seems likely that maintenance therapy will not greatly prolong the remission Continuous therapy seems essential in chronic myeloid leukemia if beneficial effect is to be maintained

Unlike aminopterin and amethopterin 6 MP has a low toxicity and can be used with little danger of added di comfort to the patient That remissions are only temporary suggests that 6 MP has more research value than clinical usefulne s Since aminopterin and amethopterin ACTH and

(6) B M J 1 1119 1124 M y 7 1955

cortisone combined with 6-MP had excellent remissions The first had two earlier successive remissions to *blood transfusion* and cortisone Almost complete remission induced by moderate doses of cortisone with 6 MP was maintained for three months In the second patient a first remission occurred with cortisone and 6 MP and was maintained on cortisone alone for two months A further combined course in moderate dosage resulted in a second striking remission *maintained for four months*

Remission has been reported in acute leukemia following acute infectious disease and this may have been a factor in contributing to or maintaining remissions in two cases in this series

X ray irradiation radioactive isotopes nitrogen mustards triethylene melamine cyanocobalamin arsenic and urethane are valueless in acute leukemia If the leukemic process remits fever anemia hemorrhage gingivitis pain glandular enlargement and other symptoms abate When radical therapy is unsuccessful control of individual symptoms becomes important in rendering the leukemic illness tolerable

The authors conclude that simple transfusion alone is likely to lead to some degree of remission within a week in about one patient in three Second remissions may occasionally be induced by this means and only when transfusion is not effective is hormone or chemotherapy indicated Then the choice of agent varies according to type of primitive cell present and the height of peripheral leukocyte count Lymphoblastic leukemias whether aleukemic or not are the most likely to respond to ACTH or cortisone Cortisone is also preferred in aleukemic myeloblastic leukemia For monoblastic leukemias and for myeloblastic leukemias with a frankly leukemic blood count which offers a ready means of day to day control of dosage 6 MP is used Folic acid antagonists though effective in many childhood leukemias have no secure place in treatment of acute leukemia in adults When a patient becomes refractory to steroids or to 6 MP a change to the other agent or a combination of both may be effective

Treatment of *Leukemia and Allied Disorders with 6 Mercaptopurine* produced complete clinical and hematologic re

pected from x ray therapy or radioactive phosphorus and superior to that obtained with other chemotherapeutic agents The gratifying improvement and the simplicity and convenience of ambulant therapy by daily oral medication free from unpleasant side effects and adequately controlled by weekly to tri weekly office visits are favorable points Myleran is regarded as the agent of choice in chronic myelocytic leukemia Its usefulness is sharply limited by its prominent myelodepressant action so that it is not only valueless but potentially harmful in chronic lymphocytic leukemia It has failed to benefit patients with acute leukemia

Clinical Trials of p (Di 2 Chloroethylamino) Phenylbutyric Acid (CB 1348) in Malignant Lymphoma are reported by D A G Galton Lyonel G Israels J D N Nabarro and Morwenna Till[8] Of 76 cases 14 were excluded because of

RESULTS OF TREATMENT WITH CB 1348 IN 62 CASES OF LYMPHOMA

D gn is	N of P tie t	Be fit	S me Effect	N Effect
H dgk d ease	23	4	14	5
R l m-cell sa coma	11	0	6	5
Lymphocytic lymphoma bl k mic	12	7	3	2
Ch ic lymphocyt leukaem	8	4	1	3
F ll l lymph m	6	5	1	0
Mycos f g des	1	0	0	1
E f l t ryth d rm	1	0	1	0
T t l	62	0	26	16

doubtful diagnosis inadequate follow up or incomplete treatment The results in the 62 remaining cases are shown in the table

In routine therapy CB 1348 which is a water soluble aromatic nitrogen mustard may be used safely if simple precautions are taken to avoid damaging the bone marrow which is especially vulnerable (1) shortly after treatment with ionizing radiations or cytotoxic drugs including CB 1348 itself (2) when infiltrated with lymphomatous tissue and (3) when hypoplastic as a result of long treatment It should not be used within four weeks after a full course of radiation or chemotherapy Whether or not treatment has been given

(8) B t M J 2 1172 1176 Nov 12 1955

cortisone and 6 MP may all produce clinical and hematologic remissions in acute leukemia it seems desirable to give patients the advantage of such chemotherapy Symptomatic relief may offer several months of useful life

Use of Myleran in Treatment of Chronic Myelocytic Leukemia in 16 patients (40 courses) is described by A Haut S J Altman G E Cartwright and M M Wintrobe (Univ of Utah) No previous therapy had been given to 11 patients 5 had been treated earlier with x rays nitrogen mustard triethylenemelamine or radioactive phosphorus Interval from apparent onset of leukemia to start of therapy was 1 56 months in seven it was a year or longer Subsequent period of observation under treatment was over two years in six and over one year in three others

When myleran (1 4 bis [methylsulfonyloxyl] butane) a sulfonic acid ester is administered in daily oral doses of 4 6 mg symptomatic improvement normalization of blood findings and reduction (in many cases disappearance) of splenomegaly can be achieved Remissions continue in some patients for 6 12 months Duration of therapy depends on individual response and generally is about 40 90 day Longest periods are required in patients with highest initial leukocyte counts Weekly to tri weekly examinations suffice to guide therapy and in most cases to prevent thrombocytopenia and pancytopenia resulting from excessive dosage

Pancytopenia occurred in this series only once Among four cases with purpura two were the only ones in which daily dose of 6 mg was exceeded Maintenance therapy has not been attempted It is simpler to continue therapy until a remission has been achieved and then to stop entirely rather than attempt to find a dose that will not produce harmful effects In cases requiring re treatment this was begun before relapse was advanced Interval between courses was always six months or over

In the four deaths in this series myleran may or may not have been implicated in two cases and definitely was not implicated in two others

Response to myleran has been at least equal to that ex

(7) A M A Arch Int Med 96 451-46 Oct b r 1955

showed positive reactions in 68% and 71% and Hodgkin s patients in 16% and 23% respectively

Immunologic response to mumps vaccination of 12 patients with Hodgkin s disease was similar to that of 14 control subjects In passive transfer of sensitivity to ragweed extract 14 patients with Hodgkin s disease reacted in the same manner as normal persons In all immediate wheals and erythema developed as with histamine

Although the group with Hodgkin s disease showed a higher mean level of serum complement than the normal group no significant changes were noted during the course of immunization Mean of the group with Hodgkin s disease was 3 07 ml $\times 10^3$ serum necessary to produce 50% hemolysis of sensitized sheep red blood cells compared with 4 40 $\times 10^3$ ml serum in the normal group

These findings indicate that the immunologic defect in Hodgkin s disease is limited unrelated to production of circulating antibody complement levels or capability of tissue to respond There was no correlation between magnitude and incidence of skin reactivity to severity and duration of Hodgkin s disease or to treatment with cortisone irradiation or nitrogen mustard Six of 12 patients with Hodgkin s disease in the antibody study received cortisone in doses to 150 mg daily during their immunization Four others received nitrogen mustard and seven irradiation Two had all three modalities Response of these patients could not be distinguished from either controls or other patients with Hodgkin s disease

This defect in immunity loss of reactivity to delayed reacting antigens may offer an explanation for the association of Hodgkin s disease with the indolent infections

On Myelofibrosis Concepts of myelofibrosis are developed by Donald R Korst Dallas V Clatanoff and Robert F Schilling [1] (Univ of Wisconsin) from a study of clinical and laboratory findings in 23 patients In 21 diagnosis was established by biopsy before death No patient known to have metastatic carcinoma or tuberculosis was included and in only one was there a history of exposure to marrow toxins

(1) A M A A h I t M d 97 169 183 F bru y 1956

persistently low neutrophil and platelet counts or peripheral lymphocytosis lead to suspicion of bone marrow infiltration If marrow puncture shows lymphocytic infiltration CB 1348 may be given but at less than standard dosage Cases of Hodgkin s disease with extensive marrow fibrosis are not suitable for chemotherapy

Standard daily dose is 0 2 mg /kg given at once without special precautions With lymphocytic infiltration or hypo plasia of bone marrow daily dose should not exceed 0 1 mg/ kg Outpatient supervision is satisfactory in less seriously ill patients but approximately weekly visits are essential It is not safe to leave a patient for over two weeks without clinical and hematologic examination Clinical improvement is usu ally evident in the third week but a four week trial i neces sary for evaluation An average course at 0 2 mg /kg /day might last four weeks (5 6 mg /kg) If maintenance therapy is given to patients who show slowly progressive improve ment during initial weeks who tolerate the drug well and whose blood picture remains stable the dose should not ex ceed 0 1 mg /kg /day and may be kept at 0 03 mg /kg Probably short courses carry less risk than maintenance therapy Although both have been effective continuous ther apy may give an illusion of maintenance to a remission that would have proceeded without further treatment

Hodgkin s Disease and Immunity were studied by W Wil son Schier Arthur Roth George Ostroff and Milton H Schrift[9] (V A Hosp Brooklyn) by (1) observations on cu taneous anergy (2) assays of development of complement fixing antibodies to mumps virus (3) passive transfer of sensitivity and (4) determination of serum complement lev els Results were compared in 43 patients with Hodgkin s disease and 79 control subjects

Cutaneous reactions to histamine were identical in the two groups The control group had 90% positive reactors to mumps antigen compared with 14% among patients with Hodgkin s disease To Candida albicans reactions were posi tive in 92% of controls and 19% of patients with Hodgkin s disease To Trichophyton gypseum and tuberculin controls

(9) Am J Med. 20 94-99 J ary 1956

is not necessarily part of the terminal picture It may exist before any therapy for leukemia Myelofibrosis may be found during the polycythemic as well as in the spent phase of polycythemia vera

Serum Electrophoretic Pattern and Morphology of Myeloma Cells Attempt at Correlation in 27 cases is reported by Wayne A Chadbourn and Horace H Zinneman (Univ of Minnesota) The cases were classified into four types of serum globulin abnormalities normal pattern (minimal protein alteration) and beta M and gamma patterns The morphologic characteristics of the myeloma cells evaluated were diameter of nucleus diameter of cell eccentricity of nucleus clumping of nuclear chromatin presence and number of nucleoli mitoses color of cytoplasm multiplicity of nuclei presence of detached masses of cytoplasm in the smear vacuoles in cytoplasm granularity of cytoplasm peripheral rim of darkly stained cytoplasm Russell bodies Mott cells presence of a Hof and rouleaux formation of red blood cells

The results showed definite significance with (1) cell diameter (2) relative area of cytoplasm and (3) ratio of diameter of nucleus to that of cytoplasm Since the nuclear diameters showed little variation and since eccentricity of the nuclei was greater when a larger amount of cytoplasm was present these three types of data are largely expressions of variations in cell diameter

The differences in total cell size clearly separated the two major groups of beta and gamma patterns Small cell size and a small amount of cytoplasm in myeloma cells were associated with the beta pattern Large myeloma cells with a large amount of cytoplasm were associated with gamma and M patterns of blood serum proteins

The findings essentially confirm Waldenstrom s previous statement that small cells associated with a beta pattern have a homogeneous cytoplasm while large cells associated with a gamma pattern have a finely mottled cytoplasm

Some clinical importance may be attached to the correlations since previous reports have established that a pro

(2) Blood 10 1109 1119 Nov mbe 1955

The typical history is of insidious development of weakness splenomegaly, weight loss and anemia Polycythemia leukemoid blood picture or gout may have been previously diagnosed Splenomegaly may have been noted for months without other symptoms A prominently enlarged nontender spleen was observed in 19 of 23 patients Frequently gross splenomegaly was out of proportion to apparent well being of the patient The liver was almost always enlarged Lymph node enlargement is not a feature of this syndrome

The hemoglobin level is commonly low but may be normal or elevated Normoblasts and teardrop shaped erythrocytes were consistently observed in peripheral blood Wide variation in total leukocyte count (2 000 200 000/cm) with a leukemoid neutrophilic distribution was the usual finding Circulating fragments of megakaryocytes were usually found their presence should arouse suspicion of myelofibrosis Unusual forms of platelets were common

Elevated BMR was found in all patients tested and hyperuricemia was not uncommon Evidence for increased rate of hemolysis was obtained in some from fecal urobilinogen measurement and reticulocyte and erythrocyte survival studies Two patients with prominent hemolytic processes had a significant reduction in anemia and hemolysis following splenectomy Bone x rays were interpreted as showing osteosclerosis in half the patients

Attempts to aspirate marrow from multiple sites usually resulted in dry taps or produced hypocellular (sinus) blood Subsequent marrow biopsy revealed patchy myelofibrosis increased thickness of bony trabeculae hyperplastic foci of myelopoiesis and often increased megakaryocytes Simultaneous marrow biopsies in a single patient may differ markedly with respect to myelofibrosis and myeloid hyperplasia Consecutive biopsies in various stages of the disease may show progression of myelofibrosis

Several patients died within two years of onset of symptoms Thus prognosis in this syndrome is not necessarily better than in typical chronic granulocytic leukemia The close relation of myelofibrosis to chronic granulocytic leukemia and to polycythemia vera is emphasized Myelofibrosis may exist in any stage of chronic granulocytic leukemia and

toma, or an altered immunization reaction The authors note that protein synthesis is abnormal in more ways than merely the production of macroglobulins Pederson was unable to demonstrate macromolecules in ultracentrifugation of multiple myeloma serums which Waldenstrom and others insist on as essential to diagnosis of macroglobulinemia Habich s study of antigenic properties of these paraproteins demonstrated through immune serums of rabbits that 14 of 16 cases were capable of developing disease specific antibodies The present case suggests a multiplicity of defects of protein synthesis e g decreased prothrombin and fibrinogen besides production of giant globulin molecules By electrophoresis globulin macromolecules can be found in gamma beta and zeta zones Mandema reported decreased prothrombin content of plasma and decreased AC globulin (Owren Factor V) Most reported cases showed pathologic amounts of euglobulin and some less than 3 Gm albumin/100 ml Several patients have had Bence Jones proteinuria Treatment has been varied because of lack of knowledge of the disease and poor prognosis At present whole blood replacement appears to offer the only hope

• [To us it seems most logical to regard this condition as an unusual type of globulin production due to a primary abnormality probably neoplastic, of plasma cell like cells The closest analogy is to multiple myeloma This idea is implicit in the cell type plasma prote n correlations attempted in the preceding article It is probably safer to predict that macromolecules will eventually be reported in multiple myeloma and Bence Jones protein in macroglobulinemia than to deny this prospect —Ed]

VASCULAR AND THROMBOCYTOPENIC PURPURAS

Dynamics of Platelet Production as Studied by a Depletion Technic in Normal and Irradiated Dogs are presented by Charles G Craddock Jr William S Adams Seymour Perry and John S Lawrence[4] (Los Angeles) Using a method of leukopheresis [described in article on p 290 this YEAR BOOK —Ed] which clears blood almost quantitatively of leukocytes and platelets by repeated frequent bleeding centrif

(4) J Lab & Cl M d 45 906 919 J e, 1955

tracted course often occurs with a gamma pattern and a more fulminating course in patients with a beta pattern

Macroglobulinemia of Waldenstrom Review of Literature and Presentation of a Case Allan E Voigt and Paul G Frick[3] (Minneapolis) cite Waldenstrom s original description (1948) of six patients whose serum proteins included a fraction presumably globulins with molecular weights near 1 000 000 (highest normal 150 000)

Man 50 was hospitalized for the fourth time in two years because of bleeding weakness and weight loss Examination showed herpes zoster ophthalmicus numerous retinal hemorrhages with engorgement of veins recent hemorrhage in both nares and oozing of blood from the site of an extracted tooth There was hepatomegaly but the spleen was not enlarged Laboratory findings were hemoglobin 7 Gm /100 ml hematocrit 21% red cells 2 170 000 white cells 7 700/cu mm Reticulocytes were under 0 3% platelet count 240 000 Sedimentation rate was 11 mm /hour and later 29 mm /hour Bleeding time was 8½ minutes Lee White coagulation time 38½ minutes Formol gel test gave positive results and the test for cryoglobulins negative results One stage prothrombin time was 18 1 (control 17 4) seconds Total serum protein was 12 Gm /100 ml (albumin 3 2 globulin 8 6 with 7 7 gamma globulin and fibrinogen 0 191 Gm /100 ml) Plasma prothrombin was decreased with decreased prothrombin consumption Vitamin K intravenously caused no decrease in one stage prothrombin time Tests for circulating anticoagulants gave negative findings Fibrinolysin was absent Factors V and VII of Owren were normal Whole blood specific gravity was 1 054 plasma 1 042 Bone marrow showed perivascular cells with resemblance between lymphocytes and plasma cells

The patient was treated symptomatically received 2 500 cc whole blood and was discharged after two weeks without definite diagnosis He was readmitted six days later comatose and nearly exsanguinated with profuse bleeding from the lower gastrointestinal tract neck rigidity hyper reflexia and Babinski reflex on the right Hemoglobin had dropped to 3 9 Gm /100 ml erythrocytes to 1 700 000 hematocrit to 12 vol % Leukocytes numbered 13 400 Erythrocyte sedimentation was 156 mm in 30 minutes and 163 mm in 1 hour Serum proteins had fallen to 7 2 Gm /100 ml (albumin 2 7 Gm globulin 4 5 Gm) Ultracentrifugation showed macroglobulins with a molecular weight of about 400 000 After receiving 9 000 cc whole blood hemoglobin rose to 13 Gm /100 ml with hematocrit of 39% One stage prothrombin times averaged 2 seconds above control

Clinical classifications of this syndrome suggested have been that it is a variant of purpura hyperglobulinemica of multiple myeloma of Bing Neel syndrome or of plasmacy

(3) A Int M d 44 419-424 F bruary 1956

toma, or an altered immunization reaction The authors note that protein synthesis is abnormal in more ways than merely the production of macroglobulins Pederson was unable to demonstrate macromolecules in ultracentrifugation of multiple myeloma serums which Waldenstrom and others insist on as essential to diagnosis of macroglobulinemia Habich s study of antigenic properties of these paraproteins demonstrated through immune serums of rabbits that 14 of 16 cases were capable of developing disease specific antibodies The present case suggests a multiplicity of defects of protein synthesis e g decreased prothrombin and fibrinogen besides production of giant globulin molecules By electrophoresis globulin macromolecules can be found in gamma beta and zeta zones Mandema reported decreased prothrombin content of plasma and decreased AC globulin (Owren Factor V) Most reported cases showed pathologic amounts of euglobulin and some less than 3 Gm albumin/100 ml Several patients have had Bence Jones proteinuria Treatment has been varied because of lack of knowledge of the disease and poor prognosis At present whole blood replacement appears to offer the only hope

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(4) J Lab & Cl Med 45 906 919 J 1955

ugation of blood and aspiration of the buffy coat followed by reinfusion of red cells and plasma The authors confirmed and extended similar observations made in 1911 by Duke who noted marked thrombocytopenia persisting three or four days in platelet depleted dogs

Use of this method in 34 dogs induced thrombocytopenia

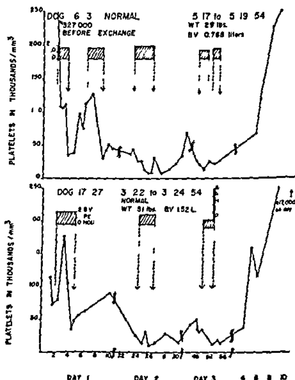
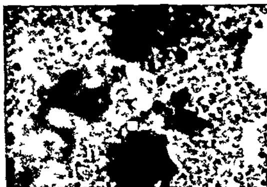


Fig 73 —Effect f epe t d l uk ph e fo th e cce s d n blood plat lets n two o m l d gs (Court sy f Craddock C G J et al J Lab & Clin Med 45 906 919 June 1955)

of 30 000/cu mm (normal mean 280 000/cu mm) in every normal animal Extent of platelet depression depended on total amount of blood cleared of platelets and was not as greatly affected as were leukocyte levels by speed of clearance Clearance of two to three blood volumes produced severe thrombocytopenia In most normal animals (Fig 73)

immediate progressive rise in blood platelets occurred after cessation of leukopheresis but the rise was transient and incomplete and sometimes absent When present it was followed by a second spontaneous fall in platelets on the second day with low values persisting on the third day Thereafter a progressive rise occurred with normal platelet counts achieved by the sixth or seventh day Whole body irradiation prevented this rise Except in a few animals receiving either heparin or dextran no purpura or hemorrhagic disorder was seen even at autopsy [However compare this



F g 4—M r w f m l d g o d y ft th day f l k ph Not m g karyocyt e d m k d mm t ty f s m f h ll (Court y f C ddock C G J s l J L b & Cl M d 45 906 919 J 1955)

with the hemorrhagic effects due to massive whole blood transfusions described in the next article —Ed]

Studies of marrow showed increased numbers of megakaryocytes particularly of immature forms noticeable by 24 hours after initial depletion Hyperplasia and immaturity became more marked over the next two days and little or no platelet production was seen in or around the immature megakaryocytes (Fig 74) Observations in a few dogs showed persistence of hyperplasia for several days after blood platelets had returned to normal

When repeated leukopheresis (on three successive days) was done on already depleted animals no further significant

blood or marrow alterations occurred and normal platelet counts returned as though additional depletions had not occurred Platelet counts after recovery were higher than initial levels and in one instance leukopheresis in this phase failed to produce thrombocytopenia

The authors consider that this prolonged thrombocytopenia after a single depletion procedure is due to inadequate platelet production by immature megakaryocytic cells Des Forges and associates observed a similar period of thrombocytopenia in patients after severe bleeding Changes in megakaryocytes produced here by removal of platelets alone without toxic or antibody effects resembled those reported by Dameshek and Miller in idiopathic thrombocytopenic purpura This lends no support to the concept of a humoral or antibody effect on marrow platelet formation for example by the spleen

• [This is work basic to our understanding of the dynamics of platelet production —Ed]

Hemorrhagic Disorder Following Massive Whole Blood Transfusions With increasing use of whole blood transfusions a variety of untoward reactions has been recognized One complication is hemorrhagic diathesis which has been noted after hemolytic transfusion reactions and after infusion of blood contaminated with bacteria More recently abnormal bleeding was noted after transfusion of unusually large amounts of compatible blood It probably is not due to hypoprothrombinemia hypofibrinogenemia platelet isoagglutinins dilution of platelets of recipient or use of wettable containers in collection and storage of blood

Julius R Krevans and Dudley P Jackson[5] (Johns Hopkins Univ) collected donor blood by gravity through plastic tubing into plastic bags containing acid citrate dextrose Coated needles were used Blood was stored at 4 C less than 21 days and was cross matched by saline and albumin cell suspensions and if there had been previous transfusion or pregnancy by the indirect Coombs technic Platelets were counted by the phase contrast method from bedside diluted samples

All of 14 adults receiving 5 500 20 500 ml blood (Fig 75)

(5) J A M A 159 171 177 Sept 17 1955

within 48 hours showed significant thrombocytopenia and 11 *showed one or more signs of abnormal bleeding*—petechiae ecchymoses mucosal bleeding hematuria Some degree of shock was noted in all and it was severe in eight Prolonged whole blood clotting time occurred in one hypoprothrombinemia in three and hypofibrinogenemia in one None of 13 patients receiving less than 5 000 ml whole

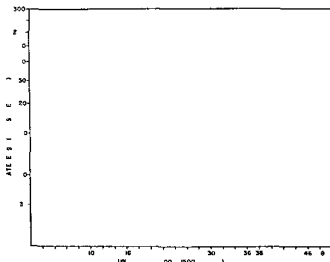


Fig 75—R l t on betw mount f blood t f ed d pl t l t l el Ab sa m t f blood dm tered w h 48 h ea h p ent 500 ml. wh l blood. O d nat low t plat let lev l ft tra f (C t y f K van J R d J ks D P J A M A 159 171 177 S pt. 17 19 5)

blood (Fig 75) in 48 hours showed hemorrhagic diathesis though 4 showed thrombocytopenia the others showed no or minimal change in platelet levels In one instance direct transfusion of blood by silicone coated syringes from donor to recipient showed a fall in recipient platelet count *from 150 000 to 121 000*/cu mm despite receipt of 500 ml whole blood containing 365 000 platelets/cu mm In five newborn infants with hemolytic disease (Fig 75) one to three exchange transfusions (500 ml blood) with type O cde whole blood less than 24 hours old produced thrombocyto

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(5) J A M A 159 171 177 Sept 17 1955

large extending ecchymotic area As ecchymosis disappeared the skin became normal Leukopenia was not observed In contrast to erythema nodosum or Osler s disease in which there is first redness and edema of the skin over the extremities then evidence of red cell leakage and ecchymosis these women had initial bleeding followed by redness swelling and extreme tenderness disproportionate to the bleeding

Three patients had abdominal pain with their painful bruises One had no recurrence of abdominal pain following splenectomy even though her distress apparently was not localized in the left upper quadrant The other two repeatedly had sharp stabbing left upper quadrant pain when ecchymotic lesions existed No pleural or abdominal friction rub was heard to suggest splenitis and local peritonitis In both x rays of the chest failed to show pleural fluid although several times the left diaphragm was elevated because of limited inspiration Histologic examination of the two spleens removed surgically showed normal tissue Two patients had no abdominal distress until they had repeated intradermal skin tests However splenitis was considered a possible explanation for the abdominal pain despite absence of splenomegaly

Two patients had episodes of intracranial bleeding they also had gastrointestinal bleeding and one had unexplained hematuria These diffuse ources of bleeding possibly may be attributed to ecchymotic like lesions but a more diffuse vascular disease cannot be excluded even though it has not been demonstrated

No specific therapy is available for this form of purpura In three of the four women this abnormal response to bruising decreased without explanation One patient had complete absence of tissue sensitivity for three year following splenectomy with recurrence of lesser degree which persisted The other splenectomized patient showed no improvement after operation but gradually lost the abnormal tissue response during the next five years and became subjectively free from painful bruising although abnormal response to intradermal skin tests with packed red cells was still present

penia Two showed abnormal bleeding tendencies Two other infants not receiving transfusions did not show thrombocytopenia despite *mild to moderately severe hemolytic disease*

The authors concluded that in these cases thrombocytopenia was related to amount of whole blood transfused and rate of infusion and could not be related to any of the previously proposed mechanisms of causation

• [In view of the clinical fact that patients with aplastic anemia sometimes show no hemorrhagic manifestations despite extremely low platelet levels and because occasional disturbances of plasma coagulation factors were reported some reservation must exist in attributing the hemorrhagic phenomena described in the preceding article entirely to thrombocytopenia —Ed]

↓ The following article presents a new clinical entity—Ed

Autoerythrocyte Sensitization Form of Purpura Producing Painful Bruising Following Autosensitization to Red Blood Cells in Certain Women Frank H Gardner and Louis K Diamond[6] (Harvard Med School) describe four women who had an abnormal response to bruising characterized by local pain swelling and extension of bleeding into adjacent areas often to a serious extent Histories and laboratory investigations suggested that these patients had tissue sensitivity to their own extravasated red blood cells All had had an episode of trauma with significant extravasation of blood which preceded onset of painful ecchymotic lesions Erythrocyte autosensitization seems an appropriate description Previous clinical observations have suggested that generalized dermal sensitivity could develop from chronic eczematoid lesions Whitfield described two female patients who had hematomas and ecchymoses following trauma and 10 days later exhibited a generalized erythematous skin eruption this was attributed to autosensitization from extravasated blood

Recurrent lesions observed in these patients may be confused with relapsing febrile nodular nonsuppurative panniculitis (Weber Christian disease) Onset of lesions is associated with erythema and induration In contrast to panniculitis none of the patients had subcutaneous atrophy or nodules Fever also was rare and associated only with a

(6) Blood 10 675-690 J ly 1955

necessary for reaction Studies for hemolysis were non contributory

Thrombocytopenia and Giant Hemangioma in Infants In 1940 Kasabach and Merritt first reported the simultaneous occurrence of these two conditions The tumor (thought to be malignant) regressed with large doses of x ray and radium implants and *platelet count returned to normal* Later reports have followed a similar pattern In a boy 4 months x ray treatment of a large hemangioendothelioma of the shoulder and neck resulted in return of a low platelet count to normal After recurrence of thrombopenia and tumor further x ray therapy over a six month period resulted in simultaneous regression of tumor and of thrombocytopenia A 5 month old infant with hemangioma controlled by superficial x ray therapy displayed no bleeding tendency and platelet count was normal at 14 months Six months later after extension of the tumor to the thorax thrombocytopenia and bleeding occurred At autopsy capillary and cavernous hemangioma and massive hemothorax were found In a 21 day old infant with thrombopenia and a capillary hemangioma fairly well localized to the left lower thigh intensive irradiation through multiple portals for 17 days caused the tumor to regress rapidly and platelets to return to normal In another infant 6 weeks with hemangioma of the thorax radium was applied to the lesion and x rays to the spleen Because thrombopenia persisted splenectomy was performed but no rise in platelet count followed Regression of hemangioma followed additional radium therapy Five months later platelet count was normal In two recently reported cases the tumor occurred on an extremity The first infant had no bleeding until about 8 months old Splenectomy was performed for thrombocytopenic purpura but failed to influence either platelet count or purpura The other child received a small dose of x rays to the tumor without apparent effect on tumor or platelets Subsequently in both patients spontaneous regression of hemangioma was associated with increase of platelet count to normal

Thomas A Good S F Carnazzo and Robert A Good[7] (Minnesota) observed three infants with large hemangio

(7) A M A Am J D Ch ld 90 260 274 S pt mbe 1955

Three patients received intradermal injections of whole blood red cells or stroma As the volume of test material was increased all had painful ecchymoses similar to those following trauma (Fig 76) Accentuation of abdominal pain after intradermal injections of red cells or stroma prevented further desensitization studies In view of this complication and the fact that tissue sensitivity gradually decreased in



Fig 76—Ecchymot le on on f arm 48 h u s after i t dermal sal e hematocrit nject ns Numbe s d at conce tr ti n of red cell injected 1=2% 2=5 % 3=10 % 4=20 % 5=40 % 6=60 % 7=80% (Courte y of Ga d e F H and D mond L K Blood 10 675 690 July 1955)

tradermal desensitization is not recommended One patient had marked subjective improvement following cortisone acetate orally

Antigenicity of the red cell is present in stromal lipoproteins and not in hemoglobin Presumably a fixed tissue antibody reacts with red cell stroma to cause edema increased capillary permeability and further extravasation of blood into tissue The lesion spreads by further contact of red cells with sensitized tissue at the periphery Gradually the lesion ceases to spread possibly extravascular tissue fluid finally decreases red cell concentration below the threshold

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(7) A M A Am J D Child 90 60 274 Sept mber 1955

epitheliomas involving the skin and subjacent soft tissues In Case 1 the tumor was on the face and neck The child died of overwhelming sepsis five months after splenectomy performed in an attempt to allay thrombocytopenia In Case 2 the tumor was on the leg bleeding episodes were so severe that amputation was contemplated Splenectomy had no effect on thrombocytopenia but after the tumor was destroyed by surgical excision and x ray treatment platelet count returned promptly to normal In Case 3 the huge hemangioma



Fig 77 —Hemangioma before x ray treatment (Courtesy of Good T A et al A M A Am J Dis Child 90 60 274 September 1955)

on the left thorax (Fig 77) was surrounded by extensive intracutaneous and subcutaneous hemorrhage over the entire thoracic cage After x ray therapy the hemangioma was completely destroyed and thrombopenia disappeared Total x ray dosage received by the last two patients was 600 r each Intense irradiation such as that described by Southard *could not have been applied to these patients* without danger of serious sequelae

In sections of these tumors obtained at biopsy surgery and necropsy large numbers of platelets were found This suggests that sequestration of platelets is occurring within

the tumor a possibility originally suggested by Southard Since the association of hemangiomas and thrombopenia has thus far been limited to infants it seems possible that an increased demand for platelets cannot be met by young children

Another possibility is that of thrombopenia due to a developmental arrest induced by a still undiscovered homeostatic regulator set in operation by excessive sequestration of platelets Removal of the major site of platelet sequestration might result in a resetting of this homeostatic regulator

• [Why so complicated an explanation employing an undiscovered regulator ? When removal of the tumor (shown to be actively sequestering platelets) amounts to removal of a filter larger and more effective than the spleen the influence on thrombocytopenia is correspondingly greater Here i at last real evidence for the effect of an accessory spleen That the so called developmental arrest of the megakaryocytes may be an appearance induced by platelet removal alone is suggested by the first article in this section —Ed]

Cases of Disseminated Lupus Erythematosus Diagnosed as Idiopathic Thrombocytopenic Purpura are described by Stanton L Eversole Jr [8]

CASE 1 —Girl 11 was hospitalized with purpura and thrombocytopenia and splenectomy was performed The platelets promptly rose to normal and the purpura disappeared and did not recur Arthritis diagnosed as rheumatoid developed a year later A year after this the characteristic facial butterfly lesion of disseminated lupus erythematosus developed and she died of staphylococcic pyemia The spleen removed at operation showed the onionpeel periarterial fibrosis characteristic of disseminated lupus erythematosus and at autopsy the kidneys showed wire loop thickening of the basement membranes of glomeruli

CASE 2 —Woman 22 five months pregnant was hospitalized with generalized purpura and thrombocytopenia She had had mild arthritis the preceding year The clinical diagnosis was idiopathic thrombocytopenic purpura At autopsy wire loop lesions were found in renal glomeruli as well as onionpeel periarterial fibrosis in the spleen She had massive fresh hemorrhage into the right cerebrum

CASE 3 —Woman 39 with purpura and thrombocytopenia had had leukopenia for several months After splenectomy the platelets rose to normal and the purpura cleared and did not recur Two years later facial butterfly skin lesions developed One year afterward she died of acute disseminated lupus erythematosus and pneumococcic septicemia No autopsy was performed The spleen removed at operation showed onionpeel periarterial fibrosis

CASE 4 —Woman 61 who had had leukopenia for nine years and

(8) B ll J h H pk Hosp 96 210 222 M y 1955

who was hypertensive and had a harsh systolic apical murmur was admitted with purpura and thrombocytopenia Splenectomy was performed for idiopathic thrombocytopenic purpura the platelet count returned to normal and the purpura subsided Postoperatively there were prolonged daily fever spikes tachycardia auricular fibrillation pericarditis and pneumonitis A transient rash developed over the chest Pathologic findings of periarterial onionpeel fibrosis in spleen and the postoperative course prompted final diagnosis of disseminated lupus erythematosus A three year follow up (by letter) revealed no subsequent symptoms attributable to this disease

CASE 5 —Woman 37 had splenectomy for thrombocytopenia and purpura which had recurred for nine years Spleen showed onionpeel periarterial fibrosis characteristic of dis eminated lupus erythematosus There was no follow up

CASE 6 —Woman 24 had splenectomy for thrombocytopenic purpura the platelet count became normal and purpura disappeared When seen 10 years later arthritis had been present 6 years Three years afterward she was brought to the hospital moribund with generalized purpura No autopsy was performed The spleen removed at operation showed the onionpeel periarterial fibrosis of disseminated lupus erythematosus

The clinical diagnosis in all these cases was idiopathic thrombocytopenic purpura and the diagnosis of disseminated lupus erythematosus was established only after splenectomy or autopsy The author has also seen numerous more recent cases in which onionpeel lesions of lupus erythematosus were present in spleen but although disseminated lupus erythematosus had been considered in the clinical differential diagnosis in some of these cases diagnosis could not be established before splenectomy The presence of disseminated lupus does not contraindicate splenectomy which may relieve purpura and thrombocytopenia

Schonlein Henoch Purpura Three Cases with Fish or Penicillin as Antigen are reported by Bendt Jensen[9] (Naestved Denmark) It is now agreed that this disease belongs to the group of allergic or para allergic disorders The allergen may be a bacterium or a bacterial product The disease is often preceded by hemolytic streptococcus infection of the upper respiratory tract and in a number of cases the antistreptolysin titer is increased The mechanism of action is the same as in glomerulonephritis and rheumatic fever

The allergen may be some article of food and in such cases

(9) Acta med sc d na 15 61 70 1955

may be found by means of cutaneous tests elimination diets and provocation experiments In two patients the allergen was fish In one of them scratch tests revealed hypersensitivity to fish and shrimp in the other responses to intracutaneous tests were negative but an elimination diet revealed the cause to be cod

Various drugs have been shown to cause Schonlein Henoch purpura and in the third patient the eruption developed after he had received three injections of penicillin Later response to an intracutaneous test with penicillin was positive

The eruption in Schonlein Henoch purpura is localized to the extensor surfaces of the extremities the cubitals the wrists and the gluteal and perigenital regions the trunk and face usually not being involved and consists of isolated fairly well defined urticarial elements measuring 0 5 2 cm at onset After a few hours the lesions become more papular and some may become confluent During the next few days they become paler and brownish They subside in one to several weeks Petechiae may occur but ecchymoses are rare

If the gastrointestinal tract is involved abdominal pain nausea vomiting diarrhea melena and hematemesis may occur The abdominal symptoms may imitate such surgical diseases as appendicitis perforated peptic ulcer etc

Joint symptoms may vary from slight pain in a single joint without swelling to intense pain and periarticular swelling of several joints The joint symptoms resemble but are less pronounced than those of rheumatic fever and the sedimentation rate and temperature rise only slightly

The most dangerous complication is involvement of the kidneys Hematuria (varying from a few erythrocytes found on microscopic examination to macroscopically bloody urine) albuminuria and cylindruria are frequent Urinary findings resemble those in acute glomerulonephritis Uremia and death may occur Severity of the kidney disorder probably depends on the nature of the allergen If the allergen is bacterial the kidney disorder will closely resemble acute glomerulonephritis in symptoms course and prognosis If it is nonbacterial (food or drug) the kidney lesion

may be less severe and more transitory The difference in allergens is probably quantitative rather than qualitative A patient with hemolytic streptococci in the throat for several weeks is exposed to a more massive influence than one who is hypersensitive to a food and is exposed to the allergen for only a few hours

As mentioned by several authors there is no doubt that certain articles of food may give rise to the disease If the allergen can be found and removed from the diet, the patient can be cured Stefanini tried ACTH treatment with good effect but transient recrudescence occurred after discontinuance and slight renal symptoms persisted and seemed indicative of chronic nephritis

• [See also last article in this section —Ed]

Hemorrhagic Diathesis with Increased Capillary Fragility Caused by Salicylate Therapy was observed in three patients by **Paul G Frick**[1] **(Univ of Minnesota)**

CASE 1 —Woman 48 had excessive bleeding after breast biopsy The only hematologic abnormalities were prolonged bleeding time and a positive Rumpel Leede test reaction for capillary fragility Hysterectomy four years earlier had revealed no abnormality to account for previous menorrhagia She had been taking 4 8 aspirin tablets daily for seven years (self prescribed) and hemorrhagic symptoms had coincided with this Tests of hemostasis repeated eight days after withdrawal of aspirin were normal Mastectomy was then performed without hemorrhagic complications

CASE 2 —Woman 66 had had hematemesis treated by blood transfusion two weeks before hospitalization She had taken aspirin intermittently for arthritis for about 20 years X ray studies of the gastrointestinal tract and tests of hemostasis were normal Since aspirin had been stopped after the episode of hematemesis a test dose (0 6 Gm three times daily) was given for four days The Rumpel Leede test became strongly positive Bleeding time was not prolonged but a subcutaneous hematoma developed at the site of skin puncture Since platelet count was normal this was attributed to increased capillary fragility

CASE 3 —Man 66 who had been taking 8 10 aspirin tablets (0 3 Gm each) for 20 years because of crippling arthritis was hospitalized for severe epistaxis (he had had several similar episodes during the past few months) and was treated by transfusion (2 000 ml) No bleeding points could be localized and blood pressure was normal Rumpel Leede test results were positive and prothrombin time was minimally prolonged An ecchymotic area developed at the site of skin

(1) Am. J M S 231 40 406 April 1956

puncture for bleeding time Nine days after withdrawal of aspirin all tests of hemostasis had reverted to normal After aspirin (0 3 Gm four times daily) was reinstated for seven days Rumpel Leede test reactions were again positive and several bleeding time determinations although not prolonged were complicated by subcutaneous hematoma at the site of skin puncture Prothrombin time remained unchanged

Salicylates in large amounts may reduce levels of prothrombin and of stable prothrombin conversion factor However the doses of salicylate taken were small and no coagulation defects or reduction of platelets were detected

These findings suggest that salicylate therapy increased capillary fragility and was the major if not the only cause of the acquired hemorrhagic diathesis So few patients develop hemorrhagic complications while taking aspirin that increased capillary fragility to aspirin seems to be a matter of individual sensitivity Salicylates should be considered as possible offending agents in any case of unexplained acquired hemorrhagic diathesis

Is Primary Hemorrhagic Thrombocythemia a Clinical Myth? William R McCabe Robert M Bird and Robert A McLaughlin (Univ of Oklahoma) report on a patient with this diagnosis in whom the presence of leukemia was eventually established They believe that evidence is insufficient in 13 previously reported cases to classify any as representing a separate disease syndrome

Man 44 had intermittent progressive numbness tingling and cyanosis of fingers transitory dizziness tinnitus scotomas occasional nausea and vomiting intermittent epigastric pain 15 lb weight loss and evidence of intestinal bleeding Examination revealed normocytic anemia slight leukocytosis marked and persistent basophilia and thrombocythemia (peak 6 200 000/cu mm) Sternal marrow showed myeloid hyperplasia with increased megakaryocytes He received x ray therapy and transfusions Five months later primary hemorrhagic thrombocythemia was diagnosed on the basis of similar laboratory findings although chronic myelogenous leukemia could not be excluded After P therapy vertigo decreased general strength improved and bowel bleeding ceased Recurring hemoptysis and a low grade afternoon fever with recurrent pain in left lower quadrant developed during the following year Examination then showed cervical and axillary lymph nodes sternal tenderness palpable liver and spleen marked leukocytosis with neutrophilic immaturity and pronounced basophilia Anemia had improved but cir

(2) An I t M d 43 18 190 J ly 1955

culating platelets were still high Four months later sternal mar row showed tremendous increase in megakaryocytes with a shift to the left in granulocytic series All symptoms became greatly aggra vated after a respiratory infection Lymph nodes enlarged and nod ules appeared in the skin these showed leukemic infiltration Periph eral leukocyte count increased to 50 000 with an extreme shift to the left Circulating platelets were normal Sternal marrow was typi cal of myeloblastic relapse of chronic myelogenous leukemia Despite additional treatment with P the patient deteriorated steadily and died two months later Necropsy findings were typical of myelog enous leukemia

The course in this case stimulated the authors to reana lyze cases previously reported as primary hemorrhagic thrombocythemia Six showed at one time pathologic ele vation of erythrocytes and thrombocythemia and can be rea sonably diagnosed as variants of polycythemia vera One patient was considered to have erythroleukemia follow up and pathologic studies were unreported In another the course suggested polycythemia vera but this diagnosis was rejected because of an atrophic spleen at necropsy this may have represented result of splenic infarcts Four patients all had marked erythrocytosis leukocytosis and thrombocythe mia Necropsy was not done in one and the others were still living One case was originally considered as myelog enous leukemia despite persistent thrombocythemia One represented a complex picture complicated by tuberculosis syphilis and typhoid Whether blast cells in peripheral blood and bone marrow represented a leukemoid reaction or true leukemia is not clear but necropsy data seemed to sup port the latter Four patients had various disorders all with increased circulating platelets none came to necropsy One of these seemed clinically to have idiopathic steatorrhea and insufficient data on the others made definitive diagno sis impossible In one case marked thrombocythemia devel oped after splenectomy and gastric carcinoma was found post mortem

Increasing evidence indicates that leukemia and perhaps other hematologic entities may exist for considerable peri ods with bizarre laboratory findings and only protracted follow up reveals the true nature of the disorder New syn dromes should not be postulated until all evidence in a given case has been carefully studied

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chronic scrutiny of various primary syndromes pancytopenia hyper splenism etc Dameshek (Bull New England M Center 16 53-63 June 1954) has emphasized the inter relationships discussed in this article under the term myeloproliferative syndromes and in our experience primary thrombocythemia has usually evolved into polycythemia or myelogenous leukemia —Ed.]

Use of Prednisone in Management of Some Hemorrhagic States is described by Mario Stefanini and Nancy B Martino[3] (Tufts College) Six patients with idiopathic thrombocytopenic purpura four with various types of acute leukemia two with aplastic anemia three with anaphylactoid purpura and seven with vascular pseudohemophilia were studied Prednisone (a corticoid hormone apparently free from some side effects of ACTH and cortisone) was given daily (0 8 1 6 mg /kg) depending on severity of bleeding

Results in idiopathic thrombocytopenic purpura varied but there was a beneficial effect on bleeding and the tourniquet test gave negative results within 48 hours in all Bleeding time was strikingly shortened in four to six days The effect on circulating platelets varied from none to a striking increase In thrombocytopenia of acute leukemia effects were similar to those observed with comparable doses of cortisone a sense of well being and temporary reduction or suppression of bleeding There was no evidence that prednisone favored control of the leukemic disease In the patients with aplastic anemia the only important effects were reduction in bleeding return to normal reactions to the tourniquet test some shortening of bleeding time and in one fleeting elevation of platelet count There was no reduction in requirement for blood transfusions In two cases of acute anaphylactoid purpura results were excellent with disappearance of all symptoms but in one chronic case there was no improvement in skin lesions the only effect was a decrease of blood edimentation rate from 62 to 28 mm in one hour and this returned to the original level two weeks after suspension of therapy In seven patients with vascular pseudohemophilia bleeding time was greatly reduced from 19 to 7 minutes within six days then to 5 minutes within two weeks Two patients had successful tonsillectomies after four to seven days treatment the drug was continued eight days after surgery and then slowly discontinued

(3) New England J Med 254 313 317 Feb. 16 1956

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Although of significant value prednisone seems less effective than cortisone or ACTH in idiopathic thrombocytopenic purpura hemorrhagic leukemia and aplastic anemia regardless of dose Conversely it is particularly effective in vascular pseudohemophilia and acute anaphylactoid purpura in low doses

Prolonged therapy with high doses was not accompanied by edema hypertension thromboembolic complications or glycosuria, nevertheless other complications such as intermittent cramping pigmentation, rash insomnia and reduction of ascorbic acid and potassium levels were observed As with ACTH and cortisone careful supervision of the patient is necessary

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COAGULATION DEFECTS

Formation of Prothrombin from Autoprothrombin by Means of Liver Mitochondria During blood clotting plasma prothrombin is not only converted to thrombin but some becomes autoprothrombin The following combinations may be sufficient for thrombin formation (1) calcium ions thromboplastin and serum Ac globulin (2) calcium ions thromboplastin and platelet accelerator (platelet factor 1) (3) calcium ions platelet factor 3 platelet cofactor I and serum Ac globulin and (4) calcium ions platelet factor 3 platelet cofactor II and serum Ac globulin These are minimum requirements adequate in isolated systems it must be assumed that many more combinations function during actual blood clotting

Norma Alkjaersig and Walter H Seegers[4] (Wayne Univ) report that autoprothrombin derived from purified prothrombin or from serum with calcium ions Ac globulin and purified platelet factor 3 can be partially reconverted to prothrombin with liver mitochondria preparations

TECHNIC —Purified prothrombin (4 ml) was mixed with 1 ml platelet factor 3 and 0 5 ml of 0 163 M $CaCl_2$ in imidazole buffer of pH 7.2 The solution contained 9 700 units of prothrombin/ml Activity declined a autoprothrombin formed After 90 minutes prothrombin was 2 810 units/ml and thrombin concentration 292 units/

(4) Am J Phy ol 183 111 113 O tober 1955

ml The solution was diluted fivefold and placed in an ultracentri fuge to remove platelet factor 3 each ml of solution was mixed with 1 ml mitochondria 0 4 ml of 0 1 M sodium oxalate and 0 4 ml veronal buffer pH 7 9 and ionic strength 0 1 A control tube con tained the same solutions except for mitochondria Within 15 min utes approximately 50% of lost prothrombin activity was recovered whereas that in the control declined further

Conversion of prothrombin to autoprothrombin could conceivably take place continuously in the circulation the only requirement would be platelet factor 3 which could presumably come from platelets The proportion of auto prothrombin in plasma is not known but is believed to be low The ratio in normal or pathologic conditions could be governed by a balance between rate of autoprothrombin formation in peripheral circulation and rate of autopro thrombin conversion to prothrombin by the liver among other factors

• [This article represents in a limited biologic system a picture of the re constitution of a factor concerned in coagulation as it perhaps occurs normally in the liver —Ed]

Failure of Synthetic 5 Hydroxytryptamine Creatinine Sulfate to Enhance Clot Retraction of Platelet Poor Human Plasma is reported by Sergio I Magalini and Mario Stefa nini (Tufts Univ) Platelet constituents with specific ef fects on hemostatic mechanism recently identified include a thromboplastic factor constituents accelerating conversion of prothrombin to thrombin and of fibrinogen to fibrin and an antiheparin factor possibly antifibrinolysin An additional substance 5 hydroxytryptamine (serotonin) liberated from platelets during clotting of human blood possesses vaso constrictor and capillary protecting activity It has also been suggested that serotonin is able to induce clot retraction of platelet poor bovine and human plasma The authors at tempted to evaluate this effect of the commercially available synthetic derivative of serotonin 5 hydroxytryptamine cre atinine sulfate use of which is currently recommended in treatment of bleeding tendency of thrombocytopenic states Ability of the compound to influence rate and extent of prothrombin conversion during clotting of platelet poor plasma was also studied

Various concentrations of commercial serotonin in a con

(5) P oc Soc E p B l & M d 90 615-617 Decembe 1955

stant volume of 0 1 ml were mixed with 0 9 ml platelet poor human plasma in both glass and silicone coated tubes There was no appreciable and constant effect on speed of clotting clot retraction and serum prothrombin activity one and three hours after completion of coagulation There was no appreciable difference 24 hours after clotting in clot retraction in tubes containing serotonin and control containing 1/10 volume saline solution Native or citrated human plasma diluted 1 5 with saline solution was mixed with varying concentrations of serotonin in a constant volume of 0 5 ml Clotting often did not occur when diluted native plasma had been made practically platelet free by centrifugation Diluted citrated plasma was clotted by addition of 0 2 ml saline containing 60 units of purified bovine thrombin Clot retraction and volume of separated serum measured 3 and 24 hours after coagulation showed that residual prothrombin activity was negligible because of high dilution and there was no demonstrable effect on retraction of the clot

Discrepancies between these findings and those of other authors possibly can be explained by difference in purity of the reagents used In view of the complexity and multiplicity of factors influencing clot retraction it is likely that without extremely careful control of all experimental conditions results may vary greatly Consequently evaluation of clot promoting activity of a drug remains hazardous

• [In view of the fact that clot retraction is a property of platelets that is readily destroyed by various procedures that do not injure other platelet functions it is not surprising that a synthetic chemical was impotent in promoting clot retraction The following article illustrates this point with a synthetic compound which unlike the serotonin derivative was active in the coagulation mechanism but, like it did not promote clot retraction —Ed]

Similarity of Action of Phosphatidyl Ethanolamine and Platelets in Blood Coagulation Work of previous investigators suggests that a lecithin like phospholipoid might be responsible for at least part of the activity of platelets in the coagulation system Robinson and Poole (1956) showed that the beneficial effect of adding chylomicrons on generation of thrombin during coagulation of rat plasma poor in platelets is similar to that of adding phosphatidyl ethanolamine (PE) and that hydrolysates of washed chylomicrons contain a

phospholipoid indistinguishable from PE These effects are so similar to certain actions of platelets that J R O Brien[6] (Portsmouth England) made a comparison of PE and platelets The only point of dissimilarity was clot retraction in which PE like boiled platelets were inactive

If PE is substituted for platelets in the normal thrombin generation test and in the thromboplastin test results are essentially the same Effect on stypven® clotting time of addition of platelets to platelet poor plasma is the same as addition of PE Both platelets and PE are inactivated by cobra venom bee venom Clostridium welchii alpha toxin and diazomethane and are absorbed by alumina

These observations suggest that the substance in platelets active in these tests is a phosphatidyl ethanolamine or some closely related compound There is an increase in circulating chylomicrons after a fatty meal and Robinson and Poole showed that chylomicrons probably contain PE Chylomicrons rapidly disappear in the postprandial period and may be broken down in the blood strem If this is so the free PE (or PE like substance) may be at least partly responsible for postprandial acceleration of blood clotting

It has also been shown in the thromboplastin generation test that alpha toxin cobra venom bee venom and alumina presumably acting on the platelet phospholipoid alone or in some combination are all capable of preventing formation of thromboplastin Intrinsic thromboplastin once formed is not inactivated If the phospholipoid molecule is incorporated in the active thromboplastin of the thromboplastin generation test it must be in some form different from that in the original platelets

Inhibition of Conversion of Fibrinogen to Fibrin by Abnormal Proteins in Multiple Myeloma was studied by Paul G Frick[7] (Univ of Minnesota) in 45 patients Ten (22%) had hemorrhagic symptoms (others have reported 7 39%) Twelve (27%) had a prolonged thrombin time but only six of these had hemorrhagic symptoms Markedly prolonged thrombin time with clot retraction absent but no thrombocytopenia caused bleeding in only two patients Two without

(6) J Cl P th 9 47 51 F bru ry 1956
(7) Am J Cl P th 25 1263 1273 Nov mber 1955

hemorrhagic symptoms had comparable prolongation of thrombin time but adequate clot retraction This suggests that bleeding occurs only if thrombin time is markedly pro longed and clot retraction absent In four patients the com bination of moderately prolonged thrombin time with mild thrombocytopenia or with cryoglobulinemia was enough to induce hemorrhage any one of these defects would probably have been inconsequential if present alone Bleeding in the presence of normal thrombin time occurred only if platelets dropped below 26 000/cu mm or in severe uremia

No direct correlation was found between prolongation of thrombin time and level of total serum proteins Although with one exception all patients with a prolonged thrombin time had total globulin levels exceeding 8 Gm /100 ml 10 patients with higher globulin elevations had normal throm bin times Therefore the anticoagulant was usually asso ciated with hyperglobulinemia but not vice versa There was no correlation between abnormal thrombin time and level of any specific globulin fraction

Information about therapy directed against the anticoag ulant is incomplete In three patients effect of the anticoagu lant became more marked as the disease progressed whereas in two treated with urethane the effect of anticoagulant de creased slightly

In two patients studied in detail the circulating anticoag ulant that delayed conversion of fibrinogen to fibrin and inhibited formation of fibrin threads with resulting clot re traction was precipitable with the beta and gamma globulins On histologic examination the clot had a gelatinous appear ance with homogeneous material interspersed between are as of red cells The well defined fibrin net of the normal clot was lacking

Shapiro (1943) first demonstrated that abnormal proteins can act as anticoagulants in multiple myeloma but did not localize the site of action The most recent studies of this clotting abnormality have been published by Uehlinger Luscher and Labhard and Craddock and associates all of whom concluded that there is an abnormal conversion of fibrinogen to fibrin Uehlinger advanced the hypothesis that abnormal protein acts as protective colloid of fibrinogen and inhibits formation of fibrin strands

Macroglobulinemia Effect of Macroglobulins on Prothrombin Conversion Accelerators Macroglobulinemia first described by Waldenstrom in 1948 is characterized by serum globulins of abnormally high molecular weight Wilde and Hitzelberger insist on the ultracentrifugation of the macroglobulins as the sine qua non for a diagnosis Clinical features of idiopathic macroglobulinemia are progressive asthenia hemorrhagic tendency (although purpura is very rare) moderate adenopathy hepatosplenomegaly and a pseudo Raynaud syndrome Leopold A Long J Luc Riopelle Marc Francoeur Armand Pare Paul Poirier Miron Georgesco and Guy Colpron[8] (Univ of Montreal) report an unusually good outcome after splenomegaly and effect of macroglobulins on blood coagulation in a woman 40

Cardinal clinical features were generalized mild lymphadenopathy of unspecified nature with concomitant weight loss asthenia and hepatosplenomegaly The spleen was enormously enlarged and showed histologically marked increase in the volume and number of the lymphoid nodules Blood study revealed hypoprothrombinemia but she never displayed any bleeding tendency Presence of antithromboplastin was ruled out and no abnormal heparin concentration could be detected in the plasma Routine prothrombin determination suggested that the blood coagulation defect concerned the yield of prothrombin and it was demonstrated that macroglobulins had an action similar to that of an antiproconvertin and an antiproaccelerin However prothrombin determination by the two stage technic showed a slight decrease not manifested by Owren s and Stefanini s technics Conversely the one stage method showed that macroglobulins had a direct effect on prothrombin conversion factors not evident in the two stage determination This discrepancy was attributed to the great plasma dilution that decreases action of foreign protein or insufficient time allotted for complete prothrombin conversion In the different experiments the yield of prothrombin was the same but incubation time in one was 5½ minutes compared to 2/ minutes for normal plasma

Paper electrophoresis of serum showed a prominent band in the gamma globulin region but unlike gamma globulin it did not move even slightly from the origin There were also minor changes in beta and in alpha globulins Dilution of the serum with distilled water caused precipitation of protein (euglobulin) which on electrophoresis remained at the origin and on ultracentrifugation showed a high molecular weight of about 19 Svedberg units

Seven months after splenectomy coagulation studies revealed no abnormality and Quick prothrombin time was 14 2/13 4 seconds Plasma showed no cloudiness in the presence of distilled water

(8) C d M A J 73 7 6 733 N 1 1955

Paper electrophoresis showed disappearance of abnormal protein with a gamma globulin fraction of normal appearance Eleven months after splenectomy very slight plasma cloudiness appeared in the presence of distilled water Quick prothrombin time was 17 9/13 8 prothrombin 14/12 1 proconvertin 19 8/13 6 and proaccelerin 19 7/11 9 *thus indicating a return of macroglobulins*

Pathologically this case is consistent with previously reported cases in which abnormal proliferation of lymphoid like cells was found This proliferation was interpreted as a variant of malignant lymphoma apparently primary in the spleen and spreading to lymph *nodes and liver Microscopically the pattern was more reminiscent* of chronic lymphatic leukemia than of lymphosarcoma Transition forms of lymphoid type cells to plasma cells a feature of sternal puncture smears could be detected only in the liver and not in the spleen where cellular multiplication seemed much more active The *process was essentially lymphoreticular proliferation* with a slight tendency to formation of plasmoid cells

• [*The reader may profitably consult articles in this* YEAR BOOK *by* Good (p 298) Chadbourn and Zinneman (p 323) and Voigt and Frick (p 324) —Ed]

Acquired Circulating Anticoagulants in Systemic Collagen Disease Autoimmune Thromboplastin Deficiency Paul G Frick[9] (Univ of Minnesota) reports three patients in whom presence of a circulating anticoagulant 4+ cephalin cholesterol flocculation and false positive blood serology were common features The first patient was a woman in *whom clinical laboratory and autopsy findings* were typical for lupus erythematosus disseminatus but L E cells were not demonstrated She gave birth to an infant in whom the anticoagulant was demonstrated for seven weeks after birth and abnormal serologic and turbidimetric test findings persisted for six months The child never displayed hemorrhagic symptoms and developed normally Another patient developed the anticoagulant while under observation after reaction to penicillin The third had lupus erythematosus disseminatus with hemolytic anemia typical L E cells were found

The anticoagulant decreased prothrombin consumption and prolonged clotting time prothrombin time and recalcification time of the first patient s and of normal blood An inhibitor of the heparin type was excluded and one of labile factor was highly unlikely Antihemophilic globulin (AHG)

plasma thromboplastin component (PTC) plasma thromboplastin antecedent (PTA) and platelet activity deficiencies were excluded as these display normal prothrombin time The patient s plasma had no effect on abnormal clotting time and prothrombin consumption of AHG PTC and PTA deficient and of thrombocytopenic blood An inhibitor of prothrombin or of stable factor of prothrombin can be excluded on theoretic grounds by marked delay in prothrombin consumption This leaves only antithromboplastin to account for the results The anticoagulant was not dialyzable It resisted heating at 60 C for 30 minutes was partially inactivated at 70 C for 10 minutes and completely destroyed at 70 C for 30 minutes The inhibitor from oxalated plasma was not adsorbed by $BaSO_4$

The tendency of patients with lupus erythematosus disseminatus to develop antibodies is well established false positive serology and positive Coombs test results are frequently found It seems highly probable that the mechanism of development of the anticoagulant is also of immunologic type Association with antigen antibody reactions and transplacental transfer in one case tends to substantiate this assumption This mechanism implies that a patient produces antibodies against antigens of his own plasma

The incidence of anticoagulants in collagen disease seems rather low Sixteen patients with lupus erythematosus disseminatus with positive L E cells nine with periarteritis nodosa three with systemic reaction to penicillin and two unclassified with multiple manifestations of hypersensitivity *were studied with anticoagulant demonstrated in only* three

Plasma Thromboplastin Component (PTC) Deficiency Produced by Prolonged Administration of Prothrombopenic Anticoagulants Investigation of effect of phenindione on the coagulation mechanism showed that patients who had received this anticoagulant for more than 30 days developed a distinctly prolonged glass clotting time Since there was no detectable change in degree of deficiency of prothrombin or of proconvertin (factor VII co thromboplastin SPCA stable factor) suspicions were directed toward the thromboplastin complex Since in previous experiments they had

excluded antihemophilic factor deficiency Herbert S Sise Delbert M Kimball and Dionysios Adamis[1] (Tufts College) investigated for presence of plasma thromboplastin component (Christmas factor antihemophilic factor B) using prothrombin consumption and thromboplastin generation as the most accurate tests available

Abnormal prothrombin consumption in a patient with PTC deficiency was corrected with normal serum and with most plasmas of patients on phenindione Plasmas of 5 of 10 patients on phenindione for 27 days or more and of 1 on dicumarol® for months however failed to correct the defect in prothrombin consumption This suggests that the factor missing in the blood of the patient with PTC deficiency was also missing in these five patients

Three individuals were selected from the group two did not correct and one did correct abnormal prothrombin consumption of the patient with PTC deficiency The thromboplastin generation test reflected the same degree of correction as the prothrombin consumption test in these cases Of three on short term phenindione one who had taken the drug for nine days showed no correction (which was unexpected) whereas the other two did It is clear that defective thromboplastin generation in the three subjects must have been due to deficiency of other than proconvertin because the other three subjects who were equally deficient in proconvertin showed normal thromboplastin generation One patient stopped phenindione and was restarted One week later when prothrombin time was 24 seconds thromboplastin generation was normal This evidence indicates that a deficiency of PTC (hemophilic factor B Christmas factor) may develop after prolonged administration of phenindione and also probably dicumarol®

Plasma Thromboplastin Component Influence of Coumarin Compounds and Vitamin K on Its Activity in Serum was studied by Richard L Naeye (Columbia Univ) Little is known about the formation of plasma thromboplastin component (PTC) first described by Aggeler *et al* in 1952 and later called Christmas factor by Biggs and co workers or

(1) P oc Soc E pe B l & M d 89 81 83 M y 1955
( ) Ib d 91 101 104 Janu ry 1956

about its disappearance from the blood Early workers dem onstrated that the level of prothrombin in blood is influenced by vitamin K and by coumarin compounds Since these com pounds also influence stable factor it is of interest to deter mine whether PTC is similarly affected

Naeye s study indicates that deficiencies of PTC are not necessarily congenital Serum levels of PTC were depressed following administration of two 4 hydroxycoumarin com pounds to 24 patients Activity of PTC was also reduced in a patient who had deficiency of vitamin K subsequent to in ability to adsorb fats (cystic fibrosis of pancreas) In both groups PTC activity rapidly increased toward normal fol lowing administration of vitamin K analogues

Thus patients with vitamin K deficiency and those re ceiving coumarin compounds develop depressed PTC activi ty this finding confirms previous observations by Sise

Stable factor and PTC have many common properties and characteristics One stage prothrombin time presents the strongest evidence that they are distinct This test detects deficiencies in prothrombin stable factor labile factor and fibrinogen but not in PTC Rabbit brain used as thrombo plastin supplies a PTC like activity artificially but human platelets used as thromboplastin do not The necessary acti vation of human platelets by PTC and other hemophilioid factors makes assay of these factors possible After further investigation PTC may prove as biologically important as are prothrombin and stable factor

Hemorrhagic Diseases of Congenital Origin are discussed by Armand J Quick[3] (Marquette Univ) To understand their mechanisms the present concept of coagulation must be considered Generation of thromboplastin generally re garded as the first step in clotting requires reaction of at least three factors (1) platelet factor (2) thromboplastino gen or antihemophilic globulin and (3) plasma thrombo plastin component or Christmas factor The resulting throm boplastin reacts with prothrombin but labile and stable factors are required in addition to produce thrombin A normal one stage prothrombin time assures that prothrom

(3) Postg d M d. 17 382 387 M y 1955

bin labile and stable factors are normal whereas a test showing normal prothrombin consumption is good evidence that platelets thromboplastinogen and plasma thromboplastin component are fairly normal in amount and quality

The prothrombin time and prothrombin consumption time are therefore valuable in study of congenital and inherited hemorrhagic diseases These include telangiectasia and Willebrand s disease (pseudohemophilia) due to vascular dysfunction both of which are uncommon Congenital hemorrhagic diseases due to coagulation defect are (1) lack of fibrinogen (2) lack of thromboplastin (hemophilia) (3) lack of plasma thromboplastin component (hemophilia B or Christmas disease) (4) panhypoprothrombinemia (type I) (5) hypoprothrombinemia (type II) (6) lack of labile factor (factor V deficiency or parahemophilia) and (7) lack of stable factor (factor VII deficiency or hypoproconvertinemia) The author confines his discussion to the third fifth and seventh defects

Besides true hemophilia due to lack of thromboplastinogen another entity closely similar both clinically and genetically is due to deficiency of plasma thromboplastin component (PTC) Among congenital diseases due to coagulation defect congenital hypoprothrombinemia vera and stable factor deficiency were not recognized as separate entities until recently In both prothrombin time is prolonged but addition of stable factor will make the test normal in stable factor deficiency but not in true hypoprothrombinemia

In hereditary stable factor deficiency the carrier i e the heterozygous individual can readily be detected by determination of prothrombin time In one family a girl with a severe bleeding tendency had a prothrombin time of 70 seconds *Her brother father mother and maternal grandfather* had slightly prolonged prothrombin times of 14 seconds The maternal grandmother s prothrombin time was the normal 12 seconds Thus it was inferred that the heterozygous grandfather transmitted the defect to his daughter who married a man also heterozygous for this defect The child received the defective gene from both parents and so was homozygous Her brother received one good and one defective gene and was therefore heterozygous like his parents

Heterozygous individuals are entirely normal clinically and can be detected only by the sensitive one stage prothrombin time determination

The genetic picture is less obvious in true hypoprothrombinemia For example two brothers with prothrombin times of 20 seconds had a definite but fairly mild bleeding tendency All other family members had normal prothrombin times Probably both parents were heterozygous and the two affected brothers received both defective genes If so it must be assumed that in respect to prothrombin deficiency heterozygous individuals cannot be detected because existing tests are inadequate

Relative frequency of true hemophilia and relative rarity of other congenital hemorrhagic diseases such as hypoprothrombinemia are readily explained Every male who inherits the defective hemophilic gene from the X chromosome will have the disease in active form All his daughters will transmit the disease to half their sons In contrast to inherit a hypoprothrombinemic state an individual must receive the defective gene from both parents Not only is this defect rare but the possibility that two persons heterozygous to the defect will marry is remote Even if they do only one of every four children born to them will be homozygous and therefore a bleeder

Plasma Thromboplastin Antecedent Deficiency Until recently males with a severe hemorrhagic diathesis characterized by prolonged clotting time normal Quick plasma prothrombin time but poor prothrombin consumption were diagnosed as having classic hemophilia This disease is still widely attributed to deficiency of antihemophilic factor (AHF) but this may be functional rather than real owing to the presence of an inhibitor (antithromboplastin) In 1952 Aggeler and co workers described a syndrome clinically and genetically indistinguishable from classic hemophilia apparently caused by absence or marked diminution of a previously unrecognized plasma constituent plasma thromboplastin component (PTC) also essential for the formation of blood thromboplastin PTC deficiency is now known as hemophilia B Christmas disease or deuterohemophilia Since PTC is adorbed by $BaSO_4$ from oxalated plasma and since aged serum

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factors are required Previous experiments demonstrated that patients plasma contained PTC and AHF and normal plasma prothrombin time indicate the presence of sufficient amounts of labile and stable factors The definitely abnormal thromboplastin generation was rectified when either the patients $BaSO_4$ plasma or serum was replaced by a similar normal preparation confirming that the missing factor PTA is normally present in both $BaSO_4$ plasma and serum and that it is indispensible for formation of effective blood thromboplastin

Three of the five disorders known to interfere with sufficient blood thromboplastin are genetically conditioned AHF and PTC deficiency are due to a sex linked characteristic and are found in the heterozygous male and in extremely rare instances in homozygous females PTA deficiency occurs in either sex It follows that after a circulating anticoagulant has been excluded PTA deficiency may be strongly suspected in a female with hemorrhagic diathesis showing prolonged clotting time and normal plasma but abnormal serum prothrombin times Objectively differentiation of the three genetic disorders can be made by simple addition tests

The exact role that PTA plays in gene action of blood thromboplastin is not yet clear However the fact that maximal PTA activity is found in the 20 33% ammonium sulfate fraction of plasma whereas corresponding fractions for AHF and PTC are the 0 20% and the 45 50% fractions respectively indicates that PTA is a definite and distinct clotting factor

Physicians must become alerted to the existence of this special type of hemorrhagic disorder Recognition especially of milder forms of PTA deficiency is of practical significance for adequate preparation of such patients for surgery

Parahemophilia (Owren) with Hemarthrosis in Two Sisters is reported by Rene Peçikyan[5] (Univ of Istanbul)

Girl 17 was hospitalized for hematologic study because of prolonged menstrual bleeding (20 days) she complained also of swelling of the knee and left elbow Abnormal bleeding and joint manifestations had begun at age 4 Her first menstrual period at 13 had required a transfusion to arrest the bleeding Her parents and an

(5) I t b 1 Cont b Cl S 3 199 10 1955

contains PTC but not AHF addition of these reagents to the patient s blood selectively corrects abnormal clotting and serum prothrombin times About 20% of cases previously di agnosed as classic hemophilia are actually PTC deficiency In 1953 Rosenthal reported another hemorrhagic diathesis resembling hemophilia which could not be classified as ei ther AHF or PTC deficiency since prolonged clotting and serum prothrombin times were corrected by both $BaSO_4$ treated plasma and aged serum Deficiency of a third throm boplastic factor plasma thromboplastin antecedent (PTA) was postulated Clinical manifestations of PTA deficiency were described as mild and occurring in either sex

Bracha Ramot Basil Angelopoulos and Karl Singer[4] (Michael Reese Hosp) report three instances of PTA de ficiency Two were in women who had had severe hemor rhages following surgical and dental procedures but no spontaneous bleeding They exhibited prolonged clotting time and normal plasma prothrombin time but abnormal serum prothrombin time and a definite decrease in thrombo plastin generation The first patient was the only one in her family so affected The mother of the second patient wa known to be a bleeder and two brothers were considered to have hemorrhagic tendency Examination showed that one was normal In the other brother results of routine clotting studies were normal but mild PTA deficiency was revealed by the thromboplastin generation test None of four children of the second patient exhibited any bleeding tendency

In Patients 1 and 2 deficiency of AHF or PTC was ex cluded by experiments demonstrating that normal $BaSO_4$ plasma normal serum and $BaSO_4$ plasma from a hemophilic patient and serum from a patient with known PTC deficien cy normalized clotting and serum prothrombin times of the patients bloods As would be expected $BaSO_4$ plasma of these patients rectified clotting abnormalities in cases of se vere hemophilia and their serums were effective in persons with severe PTC deficiency

For formation of complete blood thromboplastin interac tions of PTC AHF and platelets as well as labile and stable

(4) A M A Arch Int. Med. 95 703 712 May 1955

attention to local causes such as placenta previa premature detachment of the placenta placental retention and uterine inertia However certain severe hemorrhages result in coagulation defects and sometimes in death despite all therapy The crisis presented and the tendency to use hemostatic therapy perhaps explain why the failure of blood coagulation went unobserved for so long In 1901 DeLee first described a pseudohemophilic syndrome in a woman with severe hemorrhages and fatal uteroplacental apoplexy Dieckmann in 1936 noted the significant reduction in fibrinogen and introduced the term acquired afibrinogenemia In 1949 Moloney reported the first successful treatment with intravenous injection of human fibrinogen

Afibrinogenemia is classified according to severity The most severe cases can be treated only by intravenous injections of fibrinogen Average cases can be controlled by massive transfusions probably resulting in mobilization of hepatic reserves of glycogen Latent forms of the hematologic syndrome also exist which may be revealed only at delivery

The theories attributing the lack of fibrinogen in acquired afibrinogenemia to hepatic functional insufficiency and to lysis by a particular enzyme such as fibrinolysin or plasmin have been largely abandoned in favor of the thromboplastic theory which explains the disappearance of fibrinogen by denaturation or precipitation as fibrin i e an intravascular coagulation due to thromboplastin This theory is supported by numerous empirical observations Autopsy findings include incoagulability of the blood small islets of necrosis and visceral hemorrhage and the presence in the kidneys liver spleen heart lungs and brain of collections of fibrin obstructing the lumens of capillaries and small vessels Confirmatory experimental data have been obtained after intravenous injections in animals of amniotic fluid placental extracts and thromboplastin

When the syndrome is observed in the course of a normal pregnancy and delivery the principal etiologic factors are prolonged retention of a dead fetus amniotic embolism and premature detachment of a normally inserted placenta In all these conditions hemorrhage is caused by afibrinogene

older sister were apparently well and had never had any hemorrhages but a younger sister 11 also displayed hemorrhagic diathesis Aside from swelling and limitation of movement of affected joints the only abnormal sign was crepitant rales on auscultation of the left chest Hematologic study showed that the hemorrhagic diathesis was due principally to prolongation of prothrombin time (100 seconds) Plasma fibrinogen (190 mg /100 ml) was normal After dilution of 0 1 cc of the plasma with 0 2 cc physiologic serum the prothrombin time increased to 108 seconds but when 0 1 cc deprothrombinized plasma and 0 1 cc veronal® buffer were added the prothrombin time was reduced to 73 seconds and the deprothrombinized plasma reached values approaching normal prothrombin times Factor V (isolated according to a method described by Owren) 0 1 cc added to the patient s plasma reduced prothrombin time from 109 to 54 seconds By increasing the amount of active principle prothrombin time was finally reduced to 31 seconds using 1 cc These tests showed that the patient s blood was deficient in Owren s factor V (Quick s labile factor)

The sister 11 had displayed joint symptoms since age 5 and had had several episodes of hemorrhage (e g from a decayed tooth) and a spontaneous ocular hematoma Her prothrombin time was 85 seconds This was reduced to 25 seconds by the addition of 1 cc active factor V

The differences in and the fluctuations of clotting time in these two cases were similar to those reported in other cases of parahemophilia In the older sister the prothrombin time varied from 55 to 120 seconds indicating that she was in constant danger of hemorrhaging Pulmonary infiltration and cystic formations in roentgenograms of joints presenting hemarthrosis were consistent with the hemorrhagic diathesis These findings demonstrate that hemarthrosis is not always pathognomonic of hemophilia but may also be a sign of parahemophilia

Quick s labile factor and Owren s factor V discovered independently and prepared by different methods appear identical since both can normalize prolonged prothrombin time of old plasma and since both in the cases here described were effective in reducing abnormal prothrombin times

Hemorrhages Caused by Afibrinogenemia Acquired during Pregnancy are discussed by F Lepage L Lemerre and A Dupay[6] (Paris) Most of the severe hemorrhages in obstetric patients are satisfactorily explained and treated by

(6) Gyn et b t 54 180 03 1955

spread clinical use involves thousands instead of hundreds of therapeutic trials this unanticipated situation will occasionally develop

Under these circumstances it is seen that to apply criteria comparable in rigidity to the famous postulates of Koch to prove the toxicity of the drug is humanly—or humanely—impossible Yet because of this the accumulation of reports of observed instances of sporadic toxicity becomes worthy of the attention of the medical profession The physician must perforce weigh the therapeutic individuality and assets of the drug for his particular patient against reports of its toxicity It will not be the first time that he has been faced with the virtual impossibility of applying inadequate statistical information to the problem of the individual patient In the beginning his appraisal may be only a little better with than without such knowledge However it has been shown that the publication of one instance of suspected association usually leads shortly to reports of others if they occur when the drug is in wide clinical use Subsequent analysis may then suggest means of avoiding or mitigating the danger

With this introduction the following references to articles in the current literature relating drugs to blood dyscrasias are presented No attempt at a complete survey has been made —Ed

Aplastic anemia or pancytopenia

BERLYNE N LEVENE M AND MCGLASHAN A (Prestwich England) Megaloblastic anemia following anticonvulsants (2 cases) Brit M J 1 1247 1248 May 21 1955

BURRELL Z L JR (Milledgeville Ga) Fatal pancytopenia as a result of improperly supervised mesantoin® therapy (1 case) Am Pract & Digest Treat 6 726 728 May 1955

CALDER J *et al* (Edmonton Canada) Aplastic anemia following sulfonamide therapy (1 case) Canad M A J 74 548 Apr 1 1956

HAWKINS C F AND MEYNELL M J (Birmingham England) Megaloblastic anemia due to phenytoin sodium (1 case) Lancet 2 737 738 Oct 9 1954

ISAACSON S GOLD J A AND GINSBERG V (Brooklyn) Fatal aplastic anemia after therapy with nuvarone® (3 methyl 5 phenylhydantoin) (1 case) J A M A 160 1311 1312 Apr 14 1956

PATON M D RIDDELL N J AND STRONG G A (Edinburgh) Aplastic anemia following mepacrine treatment of lupus erythematosus (1 case) Lancet 1 281 282 Feb 5 1955

PEYMAN M A (Guildford England) Fatal case of pernicious anemia associated with chloramphenicol treatment Brit M J 1 1135 1136 May 7 1955

mia secondary to the release of thromboplastin into the maternal circulation

Amniotic embolism sometimes results from anomalous uterine contractions which should be prevented or rapidly corrected if they occur In prolonged fetal retention or premature detachment of the placenta afibrinogenemia should be suspected and the fibrinogen level and clotting time determined as a prophylactic measure The normal level of fibrinogen at the end of pregnancy is 400-480 mg/100 ml with 100 mg necessary for hemostasis If laboratory tests show deficient fibrinogen or failure of clot formation or its early dissolution curative treatment should be given Whether or not the patient is hemorrhaging she should receive intravenous injections of a total dose of 4 12 Gm fibrinogen dissolved in dextrose solution and blood volume should be restored by massive transfusion of fresh blood and plasma The prime consideration is to re establish coagulation after which natural or cesarean delivery can be managed without fear of serious hemorrhage Conversely to allow a patient *with afibrinogenemia to go into labor or to have* cesarean section without treatment may be catastrophic

• [In some of these patients there is an additional element of fibrinolysis which may be primary or secondary to hemorrhage and shock —Ed]

DRUG ASSOCIATED BLOOD DYSCRASIAS

Few useful drugs are completely free from undesirable effects in some patients Some drugs are so toxic that they are used only in the most dangerous of diseases—fire to fight fire For others early clinical experience may have shown that a valuable new agent has been found which during exhaustive laboratory tests by the manufacturer and favorable results of clinical trials as appraised by the Food and Drug Administration has exhibited no important deleterious clinical effects Nevertheless when more extensive clinical use is made of one of many such drugs it may seem that in a small number of patients it may cause injury to blood or blood forming organs If man is more susceptible to some toxic effect of the drug than any laboratory animal or if wide-

THE HEART *and* BLOOD VESSELS *and* THE KIDNEY

TINSLEY R HARRISON MD

RYAN G M S AND FORSHAW J W B Megaloblastic anemia due to phenytoin sodium Brit M J 2 242 243 July 23 1955 (See also this YEAR BOOK page 271)

SPRING M AND SOLTZ W B (Bronx N Y) Fatal aplastic anemia due to methylphenylethyl hydantoin (mesantoin®) (1 case) New York J Med 55 3478 3479 Dec. 1 1955

Agranulocytosis

FORMAN G W AND IDE L W (St Joseph Mo) Agranulocytosis associated with thorazine® therapy (1 case) Missouri Med 52 780-782 October 1955

HOLMES C R AND STONE H M (Columbia S C) Agranulocytosis due to chlorpromazine (1 case) J South Carolina M A. 52 47-45 February 1956

KENNEDY A F (Wankie Southern Rhodesia) Absolute neutrophil leukopenia after uncontrolled use of amodiaquine (1 case) Brit. M J 2 475-476 Aug 20 1955

MAHPER R A AND MARET R. (Fort Hood Tex.) Agranulocytosis complicating PAS and streptomycin therapy (1 case) U S Armed Forces M J 5 1193 1198 August 1955

MURI J W (Oslo) Agranulocytosis as complication to long term treatment with pronesthyl (1 case) J Oslo City Hosp 5 78 79 1955

PROKOPOWICZ V (Northville Mich) Agranulocytosis following chlorpromazine therapy (1 case) J Michigan M Soc 54 1468 December 1955

ROTSTEIN J FRICK P S AND SCHIELE B C (Minneapolis) Agranulocytosis associated with chlorpromazine therapy (1 case) A M A Arch Int Med 96 781 786 December 1955

TANKER J R (Northampton England) Fatal agranulocytosis during treatment with chlorpromazine (1 case) Brit M J 1 950 951 Apr 16 1955

YULES J H AND BAKER H (Boston) Agranulocytosis during chlorpromazine therapy (1 case) Bull Tufts New England Med Center 1 224 228 Oct Dec 1955

Purpura

BECKETT A G AND FOXELL A W H (London) Thrombocytopenic purpura associated with oxytetracycline therapy (1 case) Lancet 1 1053 1054 May 21 1955

GITTLER R D KISSIN M AND LITWINS J (New York) Quinidine induced thrombocytopenic purpura complicating dicumarol® therapy (1 case) Ann Int Med 42 1118 1122 May 1955

MARLEY E. (Bethlem Royal and Maudsley Hospitals England) Non thrombocytopenic purpura after administration of chlorpromazine hydrochloride (1 case) Brit M J 2 1126 Nov 5 1955

POLITOV E M (London) Thrombocytopenic purpura during chloramphenicol therapy (1 case) Brit. M J 2 106 July 9 1955

REISNER E. H JR. AND MORGAN M C (New York) Thrombocytopenia following acetazolamide (diamox®) therapy (1 case) J A M A 160 206-207 Jan 21 1956

SHMUSHKOVICH J AND DAVIS E (Jerusalem Israel) Thrombocytopenic skin purpura following treatment with trimitrin (1 case) Brit. J Dermat 67 299 302 Aug Sept 1955

PART IV

THE HEART AND BLOOD VESSELS AND THE KIDNEY

CONGENITAL HEART DISEASE

Congenital Aortic Stenosis and Its Surgical Treatment R M Marquis and Andrew Logan[1] (Edinburgh) reviewed 28 cases in which the disease was recognized in infancy or childhood average follow up period was four years Aortic regurgitation was present in six and coarctation of the aorta in three patients Five died from the lesion during the follow up period—two in infancy two before puberty and one during adolescence Six others underwent aortic valvotomy

The disease rarely presents with symptoms and is usually recognized on routine examination for other reasons Basal murmur is characteristic but a thrill may not appear for several years The apical impulse is variable and systolic pulsation at the left sternal margin is not increased The first heart sound at the lower left sternal margin and out to the apex is commonly split the aortic second sound and pulse pressure are usually normal A faint blowing aortic diastolic murmur may develop after several years

The ECG is usually normal but may show left ventricular hypertrophy and enlargement of the left ventricle may be seen by x ray

The severity of aortic obstruction determines the findings Cardiac compensation is maintained and symptoms are minimal as the force of contraction is increased The presence of symptoms suggests that the stenosis is severe and compensation inadequate Enlargement detected clinically or radiographically indicates that hypertrophy has proved inadequate and that the stenosis is severe A congenitally stenosed orifice of fixed size probably does not grow larger and decompensation may appear as the child develops

(1) B t Heart J 17 373 390 J ly 1955

ished pulmonary vasculature in roentgenograms Physiologic findings included right ventricular hypertension and a systolic gradient across the pulmonary valve Pressure tracings suggested valvular stenosis Arterial unsaturation at rest found in about 10% indicated severe stenosis

There was a significant correlation between the ECG findings of right ventricular hypertrophy and right ventricular systolic pressure All 20 patients whose right ventricular pressure was 100 mm Hg or more had one or several of the following changes R wave in V_4R or V_1 of 20 mm or over p pulmonale or abnormal right sided S T and T wave changes Of 25 patients with pressures below 100 mm Hg only 1 had an R wave in V_1 over 20 mm in height and none had S T or T wave changes

Of 21 patients subjected to Brock valvotomy 3 died all 3 exhibited congestive failure All survivors improved clinically and of eight patients catheterized after surgery seven had a satisfactory drop in right ventricular pressure

Infants with severe pulmonary stenosis in congestive failure should be operated on as soon as diagnosis is made Patients with clinical findings suggesting right ventricular pressure of 100 mm or over should be operated on at an appropriate time Patients with findings indicating right ventricular pressure below 100 mm should be observed carefully but need not be subjected to cardiac catheterization or to operation

Ventricular Septal Defects with Pulmonary Hypertension Surgical Treatment by Means of Mechanical Pump Oxygenator is reported in 20 patients by James W DuShane John W Kirklin Robert T Patrick David E Donald Howard R Terry Jr Howard B Burchell and Earl H Wood[3] (Mayo Clinic and Found) All had significant symptoms and cardiac enlargement with moderate to severe pulmonary hypertension Clinical features included a history of feeding difficulty during infancy undernutrition easy fatigability and apparent increased susceptibility to pulmonary infections Physical findings included tumultuous cardiac action a systolic thrill and a long harsh systolic murmur at the lower left sternal border with an accentuated second pulmonic heart

(3) J A M A 160 950 953 M 17 1956

Symptoms appear late in the disease and even slight disability is significant Most common is fatigue at the end of the day Exertional dyspnea is minimal Cardiac syncope is ominous and may be the precursor of sudden death Left ventricular hypertrophy detected by electrocardiography is the most reliable sign of severe stenosis

Prognosis is less good than generally believed Once the diagnosis has been made in childhood annual review is mandatory Aortic valvotomy can improve cardiac function but is likely to produce severe aortic incompetence Surgery should be limited to patients in whom the immediate prognosis is poor but it is justified if there is danger of sudden death in the presence of severe left ventricular hypertrophy rapidly progressing hypertrophy cardiac syncope dizziness or dyspnea

For good results valvotomy must be done before myocardial fibrosis and calcification of the valve develop Of six patients operated on through the left ventricular wall with an expanding dilator five developed various degrees of aortic incompetence but all six were subjectively improved at the end of six months The signs of aortic stenosis were dramatically reduced in all

• [Rapid developments are occurring in the difficult problem of aortic valve surgery as the result of the increasing use of hypothermia and of pumps to maintain the circulation It seems probable that surgical treatment both of congenital and of acquired disease of the aortic valve will be in a decidedly more favorable stage in the near future than at present. Many of the surgeons with the most experience in this field now favor the transaortic as compared with the transventricular approach—Ed]

Pulmonary Stenosis with Intact Ventricular Septum Correlation of Clinical and Physiologic Data with Review of Operative Results Benjamin K Silverman Alexander S Nadas Martin H Wittenborg Walter T Goodale and Robert E Gross (Boston) present data on 50 patients aged 3 months to 21 years (average 8 years 3 months) Predominant symptoms were severe dyspnea and fatigue with mild or no cyanosis Thirteen patients were asymptomatic

Characteristic findings included a rough systolic murmur diminished second sound at the upper left sternal border right ventricular hypertrophy in the ECG right ventricular enlargement prominent main pulmonary artery and dimin

( ) Am J Med 0 53-64 Ja ry 1956

ventricular hypertrophy on ECG in addition to right ventricular hypertrophy are better able to withstand the closure of the defect have a greater survival rate and more rapid post operative recovery

• [The results reported by the authors seem the best yet obtained by any group in regard to the difficult problem of ventricular septal defects The increased flow loads on both ventricles can obviously be relieved by successful operative treatment of the ventricular septal defect. However once the increased pressure in the pulmonary circuit has lasted for a number of years there is some question as to whether reduction of flow through the pulmonary vascular bed will cause a marked and lasting decline in pulmonary arterial pressure Further physiologic data on patients who have been successfully operated on are urgently needed to answer this important question —Ed]

Patent Ductus Arteriosus with Pulmonary Hypertension Analysis of Cases Treated Surgically is presented by F Henry Ellis Jr John W Kirklin John A Callahan and Earl H Wood[4] (Mayo Clinic and Found) Increased pulmonary artery pressures increases risk of closure of a patent ductus and risk is greatest if right to left shunt exists

The 30 patients were aged 2½ months to 59 years and half were less than 15 years Cardiac catheterization in each revealed systolic pulmonary arterial pressures above 60 mm Hg and 14 had a right to left shunt Lower oxygen saturation in the femoral artery than in the radial artery and short appearance time and abnormal initial deflection of arterial indicator dilution curves are characteristic of right to left shunt

Five patients died in the hospital and two after discharge an over all mortality of 23% but all deaths occurred among the 14 with right to left shunt a mortality of 50% Two died of hemorrhage from the pulmonary artery during surgery cause of death in the others was unknown

Hemodynamic studies during and after surgery in 17 patients revealed a fall in pulmonary arterial pressure in 14 including 3 with right to left shunt before closure Such a shunt does not preclude decrease in pulmonary arterial pressure to almost normal levels after closure and does not necessarily indicate fixed pulmonary vascular resistance In three patients pulmonary vascular resistance was lowered although not to normal Age alone does not necessarily deter

(4) J Thor ıc S g 31 68 285 M h 1956

sound Cardiac enlargement was demonstrated in all by x ray and pulmonary vascularity was increased Preoperative cardiac catheterization revealed substantial arteriovenous shunts occasional small venous arterial shunts and pulmonary hypertension Total pulmonary arterial resistance was high in nine patients and moderately increased in seven but not calculated in the other four

Repair of the ventricular septal defect in each patient was achieved under direct visualization during open cardiotomy while circulation and oxygenation were maintained by the mechanical pump oxygenator of the Gibbon type Duration of open cardiotomy varied from 10 to 45 minutes The defect was closed by direct suture in 3 patients and by insertion of a nonabsorbable polyvinyl sponge into the opening sutured to the rim of the defect in 17 The perfusion was satisfactory and the operation successfully completed in every case

Four children did not survive the postoperative stage because of pulmonary complications The clinical condition of the other 16 patients improved markedly Heaving cardiac action disappeared heart sounds became less intense the loud second heart sound diminished appetite improved weight was gained and exercise tolerance increased In most the pulmonary artery pressure decreased immediately after repair of the defect and dye dilution curves demonstrated the absence of abnormal intracardiac shunts Disturbed atrioventricular or intraventricular conduction occurred in nine patients Complete atrioventricular dissociation was seen in three patients and occurred at the time a suture was placed through the posteroinferior rim of the septal defect Sinus rhythm reappeared spontaneously in two after 5 and 10 days and the third died on the sixth day of pulmonary complications associated terminally with an inadequate ventricular rate

Children or adults with significant symptoms of ventricular septal defects associated with left to right shunts should have the defects closed even in the presence of moderate to severe pulmonary hypertension Operation should be considered in patients with small or moderate right to left shunts if there is an associated large left to right shunt and increased pulmonary blood flow Those who have definite left

were readily apparent at bedside In severe pulmonary stenosis with intact septum phonocardiography revealed a widely split second heart sound due to a diminutive pulmonary second sound widely separated from the normal aortic component In Fallot s tetralogy the second sound was usually single because the loud aortic sound was followed by an inaudible pulmonary sound If the pulmonary artery pressure was sufficiently high this delayed pulmonary second sound became recordable and even audible

One patient with severe pulmonary stenosis with an intact septum and reversed interauricular shunt had a presystolic murmur loudest in the left parasternal region This was attributed to flow through the atrial septum or the stenosed pulmonary valve during atrial systole In three patients with severe pulmonary stenosis with intact septum a loud atrial sound was heard None of the patients with Fallot s tetralogy had a similar sound

In four patients with severe tetralogy of Fallot the murmur was not intense but an early systolic sound that caused an apparent wide splitting of the first sound was heard In two patients with severe pulmonary stenosis and intact ventricular septum close splitting of the first sound and an intense clicking second component were heard

√ **Pulmonary Arteriovenous Fistula Angiocardiographic Observations in Nine Cases** are presented by Israel Steinberg and John McClenahan[6] (New York Hosp Cornell Univ Med Center) These congenital hemangiomatous malformations of the pulmonary vascular bed preferably called pulmonary arteriovenous fistulas have afferent arterial and efferent venous connections Diagnosis may be suspected in patients with cyanosis clubbing of the fingers and toes polycythemia and a murmur over a pulmonary lesion but all classic clinical findings may be absent except x ray findings

Only one of the nine patients had dyspnea cyanosis and clubbing Vascular bruits over site of the pulmonary arteriovenous fistula were heard in eight varying from a faint systolic sound accentuated by deep inspiration to a loud harsh systolic blow In one patient the bruit was present during diastole also

(6) Am J M d 19 549 568 O t b 1955

mine response to surgery and one of the most striking decreases in total pulmonary resistance occurred in a patient aged 42

All patients with patent ductus arteriosus and left to right shunts should be advised to have surgery If the shunt is predominantly right to left risk of surgery is high and closure of the ductus probably unwise If at surgery pulmonary arterial pressure falls and systemic pressure rises when the ductus is occluded closure will probably be beneficial If the reverse is true closure is hazardous

• [This study emphasizes once again the great importance of pulmonary hypertension When this functional change reached a degree great enough to cause a right to left shunt the mortality was extremely high In the absence of a right to left shunt there were no deaths in the series Since the rise in pulmonary pressure in the various conditions causing a left to-right shunt tends to be progressive the study indicates that operative procedures should be carried out at a stage when the pulmonary hypertension is still minimal or moderate and not delayed until it has become of extreme degree —Ed]

Role of Auscultation in Differentiation of Fallot s Tetralogy from Severe Pulmonary Stenosis with Intact Ventricular Septum and Right to Left Interatrial Shunt Louis Vogelpoel and Velva Schrire[5] (Cape Town Union of South Africa) examined 18 patients with tetralogy of Fallot and 6 with severe pulmonary stenosis with intact ventricular septums All had central cyanosis The two conditions must be differentiated because surgical treatment differs

Striking difference in the systolic murmur at the site of maximal intensity was found Duration of the systolic murmur relative to the second heart sound and position of maximal intensity was important In Fallot s tetralogy the systolic murmur whether soft or loud started soon after the first sound reached maximal intensity by midsystole and then diminished markedly usually ending before the single loud often palpable aortic component of the second sound In severe pulmonary stenosis with intact ventricular septum the systolic murmur was so prolonged that it extended beyond and drowned the normal aortic component of the widely split second sound It stopped before the delayed diminutive pulmonary component which was either audible or inaudible

These differences clearly shown by phonocardiography

(5) C culat on 11 714 73 M y 1955

Procaine infiltration in the region of the sinoatrial node appears to be more effective and safer than neostigmine per fusion of the coronary arteries It is easy to accomplish and requires no extensive dissection However the heart must be exposed surgically

• [The observation that infiltration of the sinoauricular node with procaine diminished markedly the tendency toward ventricular fibrillation is surprising and intriguing Its significance is not clear at present but the phenomenon obviously merits extensive investigation Such studies might well afford important information concerning practical methods of reducing one of the major hazards of cardiac surgery —Ed]

RHEUMATIC HEART DISEASE AND VALVULAR DISEASE

Effect of Intensive and Prolonged Therapy with Cortisone and Hydrocortisone in First Attacks of Rheumatic Carditis Milton Markowitz (Johns Hopkins Univ) and Ann G Kuttner[8] (New York Univ) in a combined study report on 40 patients all but one aged 4 14

One group received 300 mg cortisone or hydrocortisone daily for six weeks the dose was then gradually reduced for three weeks Seven patients were started on therapy within three weeks of onset of illness Five had normal hearts and two had residual heart disease after therapy Of three pa tients started three weeks or more after onset of illness two had residual heart disease

In a second group 300 mg was given daily for 2 days 200 mg daily for 40 days and the dose then tapered for three weeks Seven were ill less than three weeks when therapy was started Four patients with recurrence of carditis after therapy was stopped were re treated with 100 mg daily for two weeks and 50 mg daily for four to eight weeks Rheu matic activity did not occur again One patient was left with residual heart disease The other six were normal

A third group received 300 mg for 2 days 200 mg for 40 days and 50 mg daily for 2 10 months Of 15 patients treated within three weeks of onset only 2 were left with heart dis ease and 13 were normal

In all patients characteristic signs of Cushing s syndrome

(8) P d t 16 3 5 334 S pt mb 1955

The most constant finding was an abnormal shadow in the conventional chest x ray varying from minute circular densities to large sharp oval lesions Vague and ill defined edges may simulate pulmonary infiltrates Increased hilar pulmonary vasculature suggested arteriovenous fistula in two patients The fistulas may occur in any segment subsegment or lobe Fluoroscopy was never helpful

Angiocardiography provides definitive diagnosis 14 x 17 in x rays being important in discovering multiple and bilateral pulmonary arteriovenous lesions Two large films taken 2½ and 6 seconds after beginning injection usually show the pulmonary arterial and venous components of the fistula Among 2 573 injections in 1 939 patients only one death occurred and this in a woman aged 56 with pericardial effusion probably secondary to irradiation fibrosis The record fully justifies angiocardiography especially in pulmonary arteriovenous fistulas because multiple involvement must be known preoperatively to plan effective surgery and conserve lung tissue

Surgical excision is the best treatment Dyspnea cyanosis and polycythemia have disappeared following surgery Surgery has been advocated in asymptomatic patients to avoid the risk of brain abscess fatal hemoptysis or cerebral thrombosis during polycythemia—risks far greater than the morbidity and mortality of lobectomy or segmental resection

Ventricular Fibrillation in Hypothermic State I Prevention by Sinoauricular Node Blockage Hypothermia is a useful adjuvant in cardiac surgery but ventricular fibrillation is a serious hazard of this procedure Ventricular fibrillation can be induced experimentally in hypothermic dogs by occluding inflow into the right auricle or stimulating the ventricular wall or septum In an effort to protect dogs against fibrillation during such handling Angelo Riberi Harry Siderys and Harris B Shumacker Jr [7] (Indiana Univ) injected 1% procaine hydrochloride around the sinoatrial node Results were clearcut In no animal treated with procaine block did ventricular fibrillation develop whereas all of 12 not given an injection and 6 of 8 given saline instead of procaine had fibrillation

(7) An S rg 143 216 2 F bruary 1956

(Mexico City) The patients (60) were unselected except for mitral stenosis severe enough for surgery Cortisone was given to 14 and 46 served as controls During surgery a biopsy specimen was taken from the left atrial appendage of all patients and also from the pericardium of several Histologically 36 (60%) patients had active endomyocarditis 9 (15%) healing lesions and 15 (25%) healed lesions Active rheumatic lesions were less common (35 7%) and less severe in patients who received adequate doses of cortisone before surgery than in the controls (67 4%)

Past history of rheumatic activity was unrelated to the finding of asymptomatic active rheumatic lesions in the biopsy specimens Postoperative relapses occurred in 10 8% of the controls compared with 7 1% in the hormone treated group The incidence of pericarditis was 86 3% and 38 4% respectively Leukocytosis and sedimentation rate were the same in treated and untreated patients whether or not active rheumatic lesions were present

Diagnostic Value of Phonocardiography in Mitral Stenosis Mode of Production of First Heart Sound J J Kelly Jr[1] (State Univ of New York New York City) related the time of onset of the first heart sound to the simultaneous ECG reading In 100 patients with cardiac lesions of all types except mitral valve disease the mean interval of time between the Q wave and the first heart sound was 0 04 second with a standard deviation of 0 01 second In 75 patients with mitral stenosis the mean interval was 0 06±0 03 second whereas in 27 with mitral insufficiency the mean interval was 0 04±0 01 second An opening snap was found in 72 of the 75 patients with mitral stenosis

In the absence of ventricular defects the patients with mitral stenosis had a delay in the onset of the first heart sound and the degree of delay paralleled the severity of mitral stenosis This delay was diagnostic it was usually greatest in the absence of typical murmurs and no delay occurred with significant mitral insufficiency When the mitral orifice was successfully enlarged the time interval between the Q wave and the first heart sound was significantly shortened

Ventricular contraction does not contribute to the audible

(1) Am J M d 19 86 868 Dec mbe 1955

developed but subsided gradually In 11 serious side effects of hypertension infections personality changes or fluid retention were noted

Friction rubs and pericardial effusions usually disappeared during the first weeks of therapy The heart was definitely enlarged in 18 children In 10 started on therapy within three weeks heart size returned to normal of 8 treated late 4 showed persistent cardiac enlargement

Apical systolic murmurs did not change during the first few weeks but decreased or disappeared by the end of therapy that was started early Apical mid diastolic murmurs usually disappeared early in treatment Aortic diastolic murmurs occurred in four patients disappeared in two by the end of therapy and persisted in one one patient died The P R interval usually returned to normal during the first week of therapy and no new ECG abnormalities appeared

Among 29 patients treated within three weeks of onset 8 of 10 with severe 10 of 12 with moderate and 6 of 7 with mild carditis had normal hearts after therapy Of the 10 with severe carditis 3 had had congestive failure Among 11 patients started on therapy after three weeks or more had elapsed only 1 of 7 with severe carditis had a normal heart after therapy 4 had congestive failure and 1 died

If hormones are started early and in large doses patients with severe carditis do as well as those with moderate or mild involvement Residual heart disease may be decreased if cortisone is given early in doses that completely suppress the inflammatory reaction and is continued until carditis subsides

• [The results reported by these authors should be compared with the reports dealing with a much larger series (see 1955 56 YEAR BOOK p 89) Possibly the more favorable results obtained by Markowitz and Kuttner are related to the differences in dosage Final evaluation of the role of hormonal therapy in preventing cardiac complications will probably require a 10 year follow up In the mean time it seems established that such therapy tends to ameliorate the symptoms of the acute attack and that large doses should be maintained for a number of weeks Recurrence seems common when large doses are used for only a few days —Ed.]

Incidence of Asymptomatic Active Rheumatic Cardiac Lesions in Patients Submitted to Mitral Commissurotomy and Effect of Cortisone on These Lesions were studied by Javier Robles Gil Hector Rodriguez and Juan Jose Ibarra[9]

(9) Am. H rt J 50 912 9 0 Dec mber 1955

operative values and (2) much less shortening of the interval with exercise or faster return to pre exercise value

Evaluation of Present Day Surgery for Mitral Stenosis is presented by Louis A Soloff and Jacob Zatuchni[3] (Temple Univ) Evaluation is difficult because postoperative intervals are still too short for significant comparison with the long natural history of mitral stenosis a chronic illness with exacerbations unpredictable in time duration or frequency from which most patients improve Reported improvement subject to bias of physician and patient is not necessarily related to surgery Functional capacity may improve naturally or after medical treatment without surgery

The prognosis of rheumatic heart disease has steadily improved during the past century especially since introduction of antibiotics As of 1945 before antibiotic therapy 83 4% of patients aged 37 could be expected to survive to 50 only 16 6% would die before Within three years of mitral surgery in the first 500 patients mortality had already reached 16 6% and average age at death was 40 For surgery to prolong life expectancy no further deaths could occur for considerably more than 10 years Unfortunately deaths have continued

In the natural course of mitral stenosis about 8 5% of patients die of systemic embolism without heart failure Theoretically these patients should benefit from mitral valvotomy but it is difficult to predict which of them will die of embolism Only 25% of patients dying of embolism had had a preceding one Of those surviving a major embolus less than 50% had a succeeding fatal embolus The greatest difficulty is that the highest embolism rate occurs with mitral valvotomy which was the commonest cause of operative death As the natural incidence of embolism is about 1% per year performing mitral valvotomy as prophylaxis against embolism is inexcusable The claim that the chances of sustaining emboli postoperatively are quite low overlooks the high incidence of operative emboli To reduce the over all incidence of emboli to incidence occurring naturally all patients would have to be emboli free for 5 12 years postoperatively Besides most operations are done long before the age period when incidence of naturally occurring embolism is at its peak

(3) B ll New York A d Med 31 815 834 N mbe 1955

portion of the first sound the sound probably arises chiefly in the mitral valve The delay of the first sound can be explained by the disparity between the end diastolic pressures in the left atrium and left ventricle The first sound occurs when ventricular pressure equals or exceeds atrial pressure

Mitral Opening Snap in Quantitative Diagnosis of Mitral Stenosis On the assumption that the interval between the second heart sound and the mitral opening snap depends largely on the height of left auricular pressure O Bayer F Loogen and H H Wolter[2] (Dusseldorf Germany) studied 100 cases by comparative examinations with intracardiac pressure recordings and phonocardiograms Mean pulmonary capillary pressure was used as measure of left auricular pressure Systolic blood pressure in the brachial artery was also correlated with the other data

A relation was demonstrated between the interval (second heart sound mitral opening snap) and height of mean pressure in the left auricle Thus the interval shortened as mean pulmonary capillary pressure (and presumably mean left auricular pressure) increased The second heart sound mitral opening snap interval tended to shorten below 110 and to lengthen above 130 mm Hg systolic pressure Variation from the commonest range between 110 and 130 mm Hg were not common enough to allow exact definition of these parameters

The phonocardiogram permits conclusions concerning pressure increase in the left auricle which in turn is closely related to the degree of mitral stenosis Pressure increase in the left auricle for different degrees of exercise could be inferred from changes in the interval and allowed conclusions about exercise tolerance Absolute shortening after exercise and time of return to starting interval must be considered

This harmless and time saving procedure has often made preoperative cardiac catheterization unnecessary It also provides opportunity for unlimited control examinations for later evaluation of increase in exercise tolerance after mitral valvotomy

Two changes were observed after successful mitral valvotomy (1) prolongation of the interval compared with pre

(2) Am. Heart J 51 234 245 F bruary 1956

able Surgery is rarely urgent because changes occur slowly if at all in the absence of precipitating events Even repeated pulmonary edema is compatible with long free intervals The second responsibility is to determine whether simple precautionary measures may not produce a comfortable satisfactory life for the patient in respect to age and social and economic status If not and pulmonary artery pressures are high mitral valvotomy may be advised but not urged

Mitral valvotomy should never be urged Only patients with normal or slightly enlarged hearts without evidence of calcification may possibly be benefited These patients have the best natural prognosis concerning ultimate development of congestive failure and rarely die before the sixth decade Surgery on the other hand has an immediate mortality of at least 4% in this group at least 2% chance of embolism in patients surviving fibrillation and 5 10% chance of producing permanent atrial fibrillation Mitral valvotomy never destroys mitral block completely and is rarely effective in densely fibrotic and motionless valves Duration of benefit is *unknown the valve may become restenosed or the original* diagnosis may be wrong

Symptoms may appear postoperatively for the ame reasons they *appear preoperatively Active carditis arrhythmi* as infection pulmonary infarction and excessive physical strain are common causes Mitral valvotomy has been advocated early in the course of rheumatic fever because the patient will later be symptom free for longer periods if the heart is small which is true whether or not surgery is performed

Circulatory Effects of Mitral Commissurotomy with Particular Reference to Selection of Patients for Surgery are reported by M Irene Ferrer Rejane M Harvey Robert H Wylie Aaron Himmelstein Adrian Lambert Marvin Kuschner Andre Cournand and Dickinson W Richards[4] (Columbia Univ) in a study of 60 clinically selected patients willing and eager for surgery None of the patients had enlargement of the left ventricle or intractable heart failure 15 with rheumatic carditis or subacute bacterial endocarditis were rejected Of the remaining 45 15 were rejected after physiologic study 4 of the 15 had normal pulmonary artery pres

(4) C culat on 1 7 29 J ly 1955

Permanent atrial fibrillation occurs postoperatively in about 10% of patients with preoperative sinus rhythm These persons were consistently included in the group of patients improved by surgery even though digitalis previously not required is now necessary and atrial fibrillation is generally considered a more advanced stage of rheumatic heart disease Despite functional capacity assigned by the physician no patient requiring more cardiac treatment after surgery than before should be considered improved

Mitral valvotomy is often followed after a variable latent period by single or multiple bouts of pain and fever occasionally accompanied by pericarditis transient atrial fibrillation or tachycardia prolonged A V conduction and cardiac enlargement and failure and fresh Aschoff bodies can be found along the line of incision on the mitral leaflet and the pericardium—all indicative of rheumatic fever reactivity

Even if surgery decreases the A V pressure gradient without increasing the left ventricular end diastolic pressure and without diminishing cardiac output the change may not persist The leaflets may return to the prevalvotomy position calcified leaflets may limit the size of the orifice subvalvular stenosis may be unrelieved by surgery reactivation of rheumatic fever may nullify any potential benefits of surgery induced mitral regurgitation even of minor degree may be more harmful than the original mitral stenosis and the changes by surgery in valve size or mobility may be unable to increase left A V flow

Angiocardiography is not specific for mitral stenosis and left atrial emptying is impeded by this technic whether the mitral valve is stenotic regurgitant or both and may be impeded even in absence of organic valvular disease Mitral valvotomy in patients with mitral stenosis did not abolish or decrease the impediment to blood flow Results of catheterization of the right heart in predicting the degree of mitral stenosis and evaluating the effects of mitral valvotomy must also be interpreted with caution

The study suggests that present day mitral valvotomy carries a higher mortality and morbidity than that which occurs naturally The physician s first responsibility is to determine whether the symptoms are self limiting or medically treat

surotomy Pulmonary hypertension the best evidence of significant mitral block cannot be detected clinically

Objective physiologic measurements are the only reliable criteria for determining the effects of mitral surgery Subjective impressions may be unreliable

Factors Influencing Late Results of Mitral Valvuloplasty for Mitral Stenosis Laurence B Ellis and Dwight E Harken[5] (Boston) report on their first 500 patients Mean follow up was 22 months There were 58 operative deaths 2 patients were lost to follow up and the other 440 were evaluated

None of the patients was in group I—without significant symptoms 13 were in group II—without progressive symptoms most (342) were in group III—progressive symptoms and 145 were in group IV—cardiac invalids In the first 100 patients in groups II and III mortality was 14% whereas in the last 100 it was less than 3% In group IV operative mortality remained at 20 25% throughout

Moderate to marked improvement occurred in 78% 22% were unchanged or worse or died Older patients did not do as well as younger Patients with auricular fibrillation were not so often improved as those with normal sinus rhythm None of the patients had a severe grade of associated valvular disease but those with aortic diastolic or systolic murmurs as a group did less well than those without

The greatest problem was estimation of mitral insufficiency A mild degree of insufficiency did not affect ultimate good prognosis but in greater insufficiency the patients did less well Most of these patients had significant mitral stenosis which was corrected

Adverse factors were age over 40 auricular fibrillation some associated aortic valve involvement associated mitral insufficiency of moderate degree or more preoperative valve size of more than 1 sq cm postoperative valve size of less than 2 5 sq cm and calcification of the mitral valve If none of these factors was present 96% of the patients were improved If any five were present only 50% were benefited

All patients with mitral stenosis and auricular fibrillation are prone to have peripheral emboli although this is more

(5) A n I t M d 43 133 14 J ly 1955

sures and cardiac outputs at rest and the pulmonary artery pressure did not increase with exercise They had no definite physiologic abnormality but were later found to have psychiatric illness respiratory infections neurosis and alcoholism respectively

In 7 of the 15 rejected patients the difficulty was ascribed primarily to myocardial insufficiency rather than mitral block The resting pulmonary artery pressures were normal Two patients with resting pulmonary hypertension were significantly improved by digoxin Left myocardial failure had elevated the pulmonary artery pressures In the other two patients no objective evidence of disability was noted and the subjective symptoms were equivocal

Of the 31 (including a once rejected patient with cured endocarditis) who met physiologic requirements 3 refused operation and 1 was rejected because of an aneurysmal thin walled left atrium Of the 27 operated on only 8 had excellent clinical and physiologic results In each patient the resting pulmonary hypertension and the degree of rise during exercise was significantly decreased after commissurotomy although resting cardiac output was not changed dramatically

In five patients results were good clinically Two had improved physiologic findings and three were not definitely changed Another three patients were not improved clinically and physiologic studies confirmed no hemodynamic change

The other 11 patients died 6 survived surgery for varying periods of time and 5 were operative deaths Those who survived were not clinically improved and mitral block was probably not the dominant lesion Of the five operative deaths three were due to cardiac arrest one to a rent in the atrial wall and one to postoperative shock

Of the 27 patients operated on 8 should not have been offered surgery because the predominant difficulty was myocardial insufficiency and not valvular disease A double murmur in the mitral valve present in five patients with large amounts of calcium in the valve was a poor prognostic sign for successful surgery

The authors conclude that clinical criteria are inadequate for selecting patients who will benefit from mitral commis

a permanent and verifiable record of valve calcification and is harmless to the patient Atrial calcifications previously unsuspected have been demonstrated

In one patient with bouts of atrial tachycardia and cardiac enlargement of unknown etiology planigraphy demonstrated calcification of the aortic and mitral valves Valve disease had not been suspected clinically and re examination revealed no murmurs Two patients with aortic regurgitation were both shown to have mitral valve calcification and one also had aortic valve calcification In 12 patients with precordial systolic murmurs valve calcification was seen in 11 by *planigraphy all in the aortic valve 6 also had calcification* of the mitral valve

Among the 16 candidates for mitral surgery intracardiac calcification was demonstrated by planigraphy in 12 All 12 had calcification of the mitral valve 1 of the aortic valve and 3 of the atrial wall

Of the 31 patients 26 had intracardiac calcification demonstrated by planigraphy the mitral valve alone was involved in 9 the mitral valve and left atrium in 3 the mitral and aortic valves in 9 and the aortic valve alone in 5 Fluoroscopy had revealed no calcifications in three of these and incomplete findings in six Multiple valve lesions were disclosed where none or only one was suspected Valve lesions were discovered in patients with cardiomegaly or murmurs of uncertain etiology

Calcification of the mitral valve usually produces mitral stenosis and regurgitation In its presence risk of producing more regurgitation and embolism by mitral commissurotomy is increased

Cardiac Pain in Association with Mitral Stenosis and Congenital Heart Disease Douglas Stuckey[7] (Univ of Sydney) found angina pectoris in 34 (8 5%) of 400 patients with mitral stenosis Of the 26 women average age was 37 and 8 men had an average age of 33 years The angina was classic and identical to that of older patients who had coronary artery di ease except that the pain was often preceded or accompanied by breathles ness and when provoked by effort sometimes lasted for 10 minutes before relieved by rest

(7) B t H rt J 17 397 408 J ly 1955

likely if embolism has previously occurred Of 79 patients with previous embolism 71 were fibrillating at operation and 17 (24%) of the 71 had an embolism during surgery compared with over all percentage of embolization of 5 6 in group III and 16 in group IV Among a succeeding 300 patients incidence was reduced to 10% in those with preoperative emboli and to a total incidence of 2 8% in group III and 11% in group IV Danger of late peripheral emboli was low Only 6 of 442 surviving patients had emboli although more than half were fibrillating Of a succeeding 300 patients only 2 had late emboli Operation significantly reduced incidence of embolism

Changes in objective clinical findings heart size and configuration murmurs and ECG s in 106 patients were not consistent or striking and were not correlated with improved exercise tolerance

• [This report and the two preceding ones emphasize some of the differences of opinion currently prevailing concerning the problem of operations on the mitral valve Most of th published reports agree with that of Ellis and Harken in tending toward enthusiasm On the other hand one cannot neglect such critical and careful reports as the preceding two which tend to inject a note of conservatism Possibly the results obtained by different groups are related to the criteria used in selecting patients It should be remembered that many patients with organic heart disease of any type including mitral stenosis have symptoms totally unrelated to the organic disease of the heart which are dependent on coexistent anxiety and emotional disturbances It is probable that some of the favorable and also some of the unfavorable reports in the literature are confused by this fact In the experience of the editor mitral valvotomy has tended to yield good to excellent results when the patients have lacked evidence of mitral insufficiency or of aortic or tricuspid valvular disease when total transverse diameter of the heart has not been increased, when there has been clear evidence of impaired circulation through the lungs when rheumatic activity has been minimal or absent and when the rhythm has been regular —Ed]

Use of Planigraphy in Demonstration of Calcification of Heart Valves and Its Significance Louis A Soloff Jacob Zatuchni and Herbert Fisher[6] (Philadelphia) studied 16 candidates for mitral surgery and 15 with cardiomegaly or murmurs of unknown etiology

Calcification within a heart valve indicates absolute and irreversible valve disease The valve is at least partly composed of dead tissue and surrounded by a zone of avascular fibrous tissue Calcification of the mitral valve is usually accompanied by another valvular lesion Planigraphy obtains

(6) A M A A I c Med 95 219 225 February 1955

adequate coronary circulation or whether it arises in the pulmonary artery The finding of this type of pain in a number of patients with severe pulmonary stenosis constitutes evidence for the former mechanism On the other hand failure of the pain to exhibit the usual dramatic improvement following nitroglycerin administration would seem to constitute evidence against defective coronary blood flow as the causative mechanism —Ed.]

Carcinoid Cardiovascular Disease is reviewed by Victor A McKusick[8] The enterochromaffin cells of the intestine represent a diffuse endocrine gland which converts trypto phan to 5 hydroxytryptamine (5 HT) They are the parent cells of carcinoid tumors In the blood 5 HT (previously known as enteramine serotonin thrombocytin or thrombo tonin) is selectively adsorbed by platelets inactivated by amine oxidase and broken down to 5 hydroxyindole acetic acid a normal constituent of human urine The physiologic role of 5 HT is unknown but in carcinoid tumor levels are high in cirrhosis moderately low and in thrombocytopenia very low No abnormality in 5 HT has been associated with hypertension

Typical clinical features of metastasizing carcinoid are tel angiectasia of the face flushing attacks diarrhea asthma weakness and dizziness Systolic and diastolic murmurs may be inconstant The acquired valvulitis most frequently af fects the pulmonary and tricuspid valves In one of two pa tients described whose mitral and aortic valves were also involved the foramen ovale was patent The valvulitis prob ably is due to material (possibly 5 HT) elaborated by the tumor circulating in the blood and partially inactivated by lungs and liver The highest concentrations reach the right side of the heart Cutaneous A V fistulas and pulmonary or systemic hypertension may also be partially responsible for the valvulitis

Liver metastases have been present in all cases in which autopsy was done but perhaps are not essential for cardio vascular pathology The mechanism of flushing shock and cutaneous phenomena is not understood

The urine test for 5 hydroxyindole acetic acid may prove useful in recognizing cases A qualitative colorimetric test with 1 nitroso 2 naphthol can be used for screening The presence of paroxysmal or constant thrombocytosis may be helpful and x rays of the small intestine should be taken

(8) B ll. J h Hopk H p 98 13 36 J ry 1956

Generalized cardiac enlargement was present in only 4 patients the right ventricle appeared enlarged in 12 and the main pulmonary artery in 10 Electrocardiograms showed various degrees of right ventricular preponderance in 13 patients and were normal or balanced in the others

Severe pulmonary hypertension was present in seven patients who had high pulmonary resistance and low cardiac output at rest Very low cardiac outputs were found in patients both with and without pulmonary hypertension

The angina pectoris could be correlated with the severity of stenosis which was judged clinically or estimated at operation or autopsy and by low cardiac output on catheterization Clinically a low cardiac output could be anticipated by a pulse of small volume low systemic blood pressures and cold vasoconstricted extremities

Symptoms were reviewed in 100 consecutive patients with predominantly aortic valve incompetence of rheumatic origin and angina pectoris was found in 9 The ages of these nine (the youngest was 49) corresponded closely to the ages of patients with uncomplicated coronary artery disease

The congenital heart lesions were evaluated in 448 consecutive patients and angina was found in 23 distributed chiefly in three groups—6 instances in 26 patients with aortic stenosis 6 in 38 patients with severe pulmonary stenosis and 8 in 30 patients with pulmonary hypertension

Two features were common to patients with cardiac pain obstruction to circulation (severe organic stenosis of the aortic valve pulmonic valve or infundibulum or obstruction in the pulmonary arterial tree) and low cardiac output

Exercise tests in 33 patients produced changes of ischemia in the ECG s of 12 of 18 patients with cardiac pain but only slight changes in 2 of 15 controls The low fixed cardiac output did not increase adequately on exertion and the coronary blood flow was inadequate

Cardiac pain in young patients with rheumatic or congenital heart disease suggests an obstructive lesion and is an index of severity in those with aortic mitral or pulmonary stenosis

• [This type of pain has in the past been designated as hypercyanotic angina or as pulmonary hypertensive pain There has been some question whether the pain actually arises in the myocardium and is related to in

tagonists against serotonin suggest that an antagonist might by neutralizing or blocking its effect relieve symptoms It is less likely but possible that as an antagonist against the product of a tumor it might inhibit its growth Clues yielded by valvular lesions in these cases may help to illuminate some aspect of valvular disorders of the heart in general

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HYPERTENSION

Treatment of Hypertension with Modern Drugs in severe stages of the disease as carried out by Henry A Schroeder and H Mitchell Perry Jr [1] has been confined largely to oral combination of hydralazine and methonium compounds The chance of harming the patient with drug therapy is small if minimal precautions are observed Drug induced hypotension is transient There has been no evidence of myocardial anoxia and the syncope that accompanies cerebral ischemia responds readily to the supine position No permanent damage from clots or oxygen deficit has been observed Drug induced parasympatholysis may lead to obstruction of hollow viscera Parasympathomimetic drugs catheterization or even prostatectomy may be needed to control urinary retention in prostatism Paralytic ileus from methonium therapy has not been seen Laxatives can be used to control the bowels Unpleasant side effects diminish and except for masculine impotence finally vanish after many months

The greatest dangers to life have involved cessation of therapy in severe and malignant stages 40% of patients in the former and all in the latter stages have died of complications of hypertension when therapy was stopped These figures compared to total mortality of under 4% for severe *benign and 14% for malignant stages treated adequately* indicate that therapy once begun should be continued

The authors practice is to bring the blood pressure to normal with drugs even in early stages Patients are watched carefully for toxic reactions and new symptoms are attributed to the drugs Treatment is mandatory in the malignant or accelerated stage of hypertension and is essential

(1) C lat 13 98 112 J ry 1956

As much malignant tumor should be removed as possible including hepatic metastases The pathologic process in the heart valves uncomfortable attacks of flushing asthma and diarrhea and profound weakness can perhaps be kept at a minimum by surgically reducing the total tumor mass Survival after palliative surgery despite metastases may be long The tumor is rarely radiosensitive Serotonin antimetabolites now available probably are not helpful

Syndrome of Carcinoid and Acquired Valve Lesions of Right Side of Heart William B Bean David Olch and Harry B Weinberg[9] (State Univ of Iowa) report two cases of this rare interesting syndrome

CASE 1—Woman 42, displayed typical clinical features of patterned irregular flushing which came and went abruptly mottled cyanosis diarrhea asthma signs of valvular lesions of right side of heart edema and congestive failure She first had diarrhea with abdominal cramps which persisted and about six months later recurrent erythema over the trunk abdomen and face began Skin of the lower abdomen back and legs was continously cyanotic She lost 40 lb Petechia heart signs and edema appeared later and downward course was rapid

Autopsy showed malignant carcinoid of the ileum with metastases to the liver Tricuspid mitral pulmonic and aortic valves and tendinous cardiac cords were thickened Despite marked sclerosis of the valves no lesion of rheumatic fever was found

CASE 2—Man 43 had flushing signs two months after appendectomy with later dyspnea and edema He displayed a progressively deteriorating course similar to that observed in Case 1

Autopsy revealed malignant carcinoid of the ileum with metastases to liver lymph nodes and posterior parietal peritoneum Valvulitis involved all cardiac valves but was most marked in pulmonic and tricuspid As in the first patient telangiectasia with proliferative and thrombotic disorganization of blood vessels in the skin was noted.

Lembeck has recently demonstrated production of serotonin by carcinoid tumors The possible mechanism by which a potent vasodilating substance manufactured in the liver thrown suddenly in potent concentration into the right side of the heart might damage directly the mural endocardium and tricuspid and pulmonary valves is speculative Waves of vasodilatation clinically suggest irregular intermittency and varying concentrations of the agent that must traverse at least the pulmonary capillaries and perhaps those of the liver Wooley s studies on biologic and molecular an

(9) Circulation 1 1-6 July 1955

tagonists against serotonin suggest that an antagonist might by neutralizing or blocking its effect relieve symptoms It is less likely but possible that as an antagonist against the product of a tumor it might inhibit its growth Clues yielded by valvular lesions in these cases may help to illuminate some aspect of valvular disorders of the heart in general

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HYPERTENSION

Treatment of Hypertension with Modern Drugs in severe stages of the disease as carried out by Henry A Schroeder and H Mitchell Perry Jr [1] has been confined largely to oral combination of hydralazine and methonium compounds The chance of harming the patient with drug therapy is small if minimal precautions are observed Drug induced hypotension is transient There has been no evidence of myocardial anoxia and the syncope that accompanies cerebral ischemia responds readily to the supine position No permanent damage from clots or oxygen deficit has been observed Drug induced parasympatholysis may lead to obstruction of hollow viscera Parasympathomimetic drugs catheterization or even prostatectomy may be needed to control urinary retention in prostatism Paralytic ileus from methonium therapy has not been seen Laxatives can be used to control the bowels Unpleasant side effects diminish and except for masculine impotence finally vanish after many months

The greatest dangers to life have involved cessation of therapy in severe and malignant stages 40% of patients in the former and all in the latter stages have died of complications *of hypertension when therapy was stopped These* figures compared to total mortality of under 4% for severe benign and 14% for malignant stages treated adequately indicate that therapy once begun should be continued

The authors practice is to bring the blood pressure to normal with drugs even in early stages Patients are watched carefully for toxic reactions and new symptoms are attributed to the drugs Treatment is mandatory in the malignant or accelerated stage of hypertension and is essential

(1) C rc lation 13 98 112 J uary 1956

for prolongation of life when there has been one cerebral accident or congestive heart failure Otherwise it is elective although often it should be strongly urged

No patient has proved totally resistant to combined hydralazine and methonium compounds sometimes doses required are very large In the presence of renal damage hypertension can be merely modified since normotension is incompatible with adequate glomerular filtration and therefore with life Occasionally considerable tolerance occurs in patients who have begun therapy and then discontinued it If the drug is reinstated two three or even many times the original dose may become necessary Conversely tolerance has not developed when these drugs were properly used and normotension or a reasonable facsimile was achieved for long periods in fresh untreated case Eventually smaller quantities of hydralazine and methonium compounds are needed At the end of a year of treatment 79 unselected patients who had maintained diastolic pressures below 100 mm Hg with these two drugs alone took only 73% of the initial doses of blocking agent after two and three years required percentages were 57 and 46 respectively Diminution in hydralazine intake was only slightly less A few have been able to discontinue drugs entirely while some are controlled with reserpine alone and some with a combination of reserpine and hydralazine Patients whose diastolic pressures consistently exceeded 100 mm Hg required the original doses of both agents to maintain even inadequate blood pressure control

Malignant stages of hypertension show the efficacy of therapy In a recent compilation average life expectancy without therapy was 9 months with almost half the subjects succumbing in 90 days and only 15% surviving for 2 years Among 64 of the authors patients in the malignant stages who have regularly taken hydralazine and hexamethonium chloride for two to four years 54 are alive and 51 are working

There is no tendency to cerebral hemorrhage when blood pressure is well controlled but cerebral thrombosis may occur when normotension is induced too fast Blood cholesterol levels usually fall rapidly and remain lower for years in most patients taking hydralazine Angina pectoris usually gets better but occasionally becomes immediately worse probably on a hemodynamic basis Heart fail-

disappeared as a cause of death in the authors series A failing left ventricle can be relieved by parenteral autonomic blocking provided elevated blood pressure contributes significantly to the cardiac load to the extent that digitalis is no longer needed

Patients who do not respond well to medical treatment include un co operative persons those with severe azotemia and those with systolic hypertension on an athero sclerotic basis with normal diastolic pressure Slight azotemia is compatible with an excellent clinical result Sixteen patients with moderate nitrogen retention are alive after three years

Serious late sequelae may result from hydralazine (arthralgia which ultimately becomes indistinguishable from disseminated lupus erythematosus) and from hexamethonium chloride (interstitial fibro is of lungs observed particularly in azotemic patients with malignant hypertension following extended use of the drug) These complications can usually be avoided or aborted in early stages if patients are carefully examined every three months

The present concept of therapeutic rationale is that hydralazine counteracts the renal factor whereas ganglionic blocking agents affect the autonomic nervous system or neurogenic factor The authors speculate that hydralazine attacks the mechanism by which some nonessential metal inhibits a metalloenzyme in the kidney concerned in alteration of intermittent vasospasm into permanent vasospasm eventually producing organic changes in the kidney which maintains high blood pressure

Treatment of the Ambulatory Hypertensive Patient with Pentolinium Tartrate Method for Regulating Dosage is described by Samuel Waldman and Louis Pelner[2] (Brooklyn) The drug satisfactorily reduces blood pressure in patients with severe or moderately severe hypertension but meticulous adjustment of the dose is most important Pentolinium tartrate is a ganglion blocking agent with a more predictable definite and prolonged effect than that obtained with hexamethonium

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( ) Am J M Sc 231 140 150 F bru 1956

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( ) A J M S 31 140 150 F b u y 1956

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Use of Pentolinium Tartrate with and without Hydralazine in Treatment of Severe Hypertension is reported by H Mitchell Perry Jr and Henry A Schroeder[3] (Washington Univ) Pentolinium tartrate a pentamethonium derivative with two terminal quaternary nitrogen atoms in a pyrrolidine ring is an autonomic blocking agent like its parent compound but acts longer has a greater effect on blood pressure and less effect on gastrointestinal motility

Patients without prior treatment initially received 20 mg pentolinium tartrate every six hours Every day the dose was increased by 20 mg until blood pressure fell appreciably This dose was then given every four hours for any sitting systolic pressure exceeding 140 A half dose was given for pressures of 130 140 and a quarter for pressures of 120 130 Then hydralazine was added in increasing amounts to minimize fluctuations and prevent tolerance to the drug 20 mg pentolinium tartrate replaced about 125 mg hexamethonium chloride

Man 39 hospitalized with dyspnea and precordial pain had blood pressure of 246/148 retinal hemorrhages exudates and papilledema cardiomegaly albuminuria and hematuria Urine specific gravity was 1 015 pyelograms were normal and he had no azotemia

Within three days hexamethonium chloride orally dropped blood pressure to 150/90 Because of nausea distention and asthenia he refused further therapy and was discharged on daily dose of 500 mg hydralazine and 100 mg Rauwolfia serpentina

Five months later he was readmitted in severe congestive failure grade 4 hypertensive retinitis blood pressure of 240/140 with azotemia and anemia He again refused combined hexamethonium and hydralazine and was discharged improved on digitalis and 1 500 hydralazine and 1 mg reserpine daily

He was admitted three weeks later in severe congestive with anasarca oliguria Cheyne Stokes respirations and ır azotemia He now agreed to pentolinium orally The dose was ually increased to 2 500 mg in divided doses daily plus a maxır of 300 mg hydralazine every four hours Sitting blood ı to 135/95 Blood pressure was maintained at 170/110 on an of 200 mg hydralazine and a maximum of 300 mg pentolinium trate orally six times daily

At dis harge he had lost 14 5 kg congestive failure had c' nonprotein nitrogen level was 27 mg /100 cc exudates and ledema were much less noticeable and he had no fresh retinal I rhages Four months later he was working and felt well Mean pressure was 155 and mean daily intake of pentolinium tartrate hydralazine was 929 and 1 000 mg

(3) New E gl d J M d 252 1057 1066 J 23 1955

pulse pressure is narrower When patients are given sufficient pentolinium this vasoconstrictive reflex is blocked and the pressures are higher in recumbency than in the sitting position Of 100 unselected normal and hypertensive patients 85 had higher pressures both systolic and diastolic when seated than when recumbent and in 10 the pressures were the same Veratrum or reserpine did not affect this status

Pentolinium can be administered until the postural vasoconstrictive reflex is abolished and pressures are higher lying than sitting Beyond this point the dose should be increased only cautiously or not at all depending on the level of blood pressure obtained and desired The dose should be increased if the pressure is elevated above the desired level in the sitting and reclining positions with no change on reclining or if it is elevated in the upright position and decreases with recumbency The dose should be the same or increased cautiously if the blood pressure rises on reclining If the pressure is normal or low in the sitting position and remains the same when the patient reclines the same dose should be maintained If it is normal with recumbency and falls when the sitting position is assumed the dose should be decreased

Pentolinium should be administered initially in 10 20 mg doses three times daily one half hour before meals and increased in 10 20 mg increments per dose An additional dose may be given at bedtime to potentiate the evening dose and maintain lower pressures during sleeping hours Sudden interruption of all doses should be avoided to prevent precipitous dangerous rises in pressure Reserpine 0.25 mg three times daily after meals enhances the effect of pentolinium and decreases the incidence of side effects

Side effects include postural hypotension dryness of the mouth blurred vision constipation and occasional impotence in the male Potentiation of the action of pentolinium is noted after ingestion of alcohol exercise salt depletion meals hemorrhage or during exposure to heat or hot weather Rigid salt restriction is not necessary

Of 26 patients treated by this method all had significant falls in systolic and diastolic blood pressure both seated and recumbent Cardiac retinal and coronary status was improved whether or not blood pressure approached normal

Treatment of Hypertensive Emergencies Parenteral Use of Reserpine was studied by R W Griffin J W Stover and R V Ford (Baylor Univ) in 12 men aged 29 68 whose diastolic blood pressure in the recumbent position was 110 mm Hg or higher All received a standard diet containing 800 mg sodium and remained at bed rest Any digitalis antibiotics or other medications were continued Fifty intramuscular injections of reserpine were given 16 of 2 5 mg 25 of 5 mg and 9 of 10 mg The blood pressure decreased in all 50 trials dropping 20 mm or more in 46 Usually there was a noticeable drop within 90 minutes of injection

In none of the 50 trials was an allergic or anaphylactic reaction noted The commonest side effect was somnolence occurring eight times Three patients were intermittently comatose Nasal congestion and diarrhea were each noted once Anxiety occurred in four patients and was severe in two The electrocardiograms and renal function of all 12 patients remained unchanged

The maximal effect was achieved by 2 5 mg reserpine Average onset of effect was 3 hours and the usual duration was a little over 10 hours at this dose The blood pressure decline is smooth without marked variations and results are predictable

Reserpine 2 5 mg intramuscularly every 12 hours is recommended as adequate treatment for hypertensive crises

CORONARY DISEASE

Anterior Chest Wall Syndrome—Chest Pain Resembling Pain of Cardiac Origin is described by Myron Prinzmetal and Rashid A Massumi[6] (Univ of California Los Angeles) Innumerable noncardiac conditions visceral and somatic cause anterior chest pain which may be confused with pain of coronary origin

This symptom complex consists of pain in anterior wall structures with exquisite tenderness on fingertip pressure It is common after coronary occlusion but may occur in normal individuals Histologically the changes are inconsis

(5) New England J Med 254 593 598 M 29 1956
(6) J A M A 159 177 184 Sept 17 1955

In 24 patients in severe stages of hypertension pentolinium tartrate and hydralazine controlled the worst cases if started before frank uremia appeared Although quantitatively more potent in its effect on blood pressure pentolinium tartrate was qualitatively similar to other methonium compounds It sometimes produced marked variations in systolic pressures In six patients with collagen disease following hydralazine pentolinium tartrate combined with other drugs produced varying results

Combined Chlorpromazine Rauwolfia Serpentina Therapy in Essential Hypertension Preliminary Report Chlorpromazine a nonbarbiturate central depressant agent depresses motor activity is an antiemetic has mild adrenolytic activity is occasionally hypotensive is slightly antihistaminic intensifies and prolongs the duration of action of narcotic analgesics sedatives and anesthetics and is a muscle relaxant Rauwolfia acts directly on the hypothalamus and inhibits the sympathetic system It has been extensively used in essential hypertension

Harold B Eiber[4] (New York Med College) treated 75 patients with oral doses of 15 mg chlorpromazine combined with 50 mg Rauwolfia serpentina (whole root) three times daily More than 85% of the patients with mild hypertension had noticeable lowering of blood pressure more than 70% with moderate hypertension were benefited and more than 60% with severe hypertension were improved Subjective improvement occurred in 95% with less anxiety less head fulness and less headache Maximal hypotensive response was observed in most patients in two or three weeks

After 10 14 days of placebo replacement the blood pressure readings of almost all the patients increased to control levels Combined chlorpromazine rauwolfia therapy was more effective than treatment with either preparation alone

With this dosage schedule the duration of hypotension was approximately six to eight hours No side effects and no jaundice occurred during 18 months of therapy

Following this study a total of 350 patients were treated Results were even more promising with a dosage schedule of 25 mg chlorpromazine combined with 25 mg Rauwolfia serpentina (whole root) orally three to four times daily

(4) J A M A 158 30 731 July 2 1955

The anterior chest wall syndrome is common and its recognition is of great practical importance All patients who have anterior chest pain particularly if they have a history of myocardial infarction should be examined carefully for tenderness of the chest wall Therapeutic tests are harmless and may be diagnostic

• [When a patient with pain arising in the anterior chest wall happens to have innocent electrocardiographic changes resulting from anxiety healed pericarditis a healed contusion etc the diagnosis of coronary disease is commonly made This results in unjustifiable restriction of activity and unnecessary anxiety on the part of the patient and family In most instances the skeletal pain arising in the anterior chest does not require treatment other than reassurance and perhaps an occasional local injection of procaine Only in the more severe instances is hormonal therapy necessary Once the patient is convinced that the pain has nothing to do with the heart the problem tends to solve itself

It should be emphasized that this type of skeletal pain arising in the chest is analogous to the hand shoulder syndrome It may occur in persons with no cardiac disease whatever but is particularly common in those who do have coronary artery disease Its presence should therefore lead to a careful search for evidence of angina pectoris or of a previou myocardial infarction In any case the patient should be strongly reassured concerning the lack of significance of this particular type of pain —Ed]

Heart Muscle and Electrocardiogram in Coronary Disease III New Classification of Ventricular Myocardial Damage Derived from Clinicopathologic Findings in 100 Patients (Part Two) is presented by John J Sayen Warner F Sheldon and Charles C Wolferth[7] (Philadelphia) All patients had severe narrowing of at least one major coronary artery and 87% had more than one vessel severely obstructed In many instances of severe narrowing or old occlusion, no scar was found in the region supplied by that vessel Incidence of old occlusion or narrowing was nearly the same for all three coronary arteries about 85% Recent thrombi were about a third as frequent as old lesions with the left circumflex artery less often involved than the other two

Myocardial damage old or recent was confined to the distribution area of one coronary artery in 42 patients In 56, two or three coronary regions were involved and in 2, no damage was found Isolated small muscle lesions were frequent in the posterior and lateral regions of the left tricle Large isolated anterior lesions were occasionally but small anterior lesions were always associated with er usually older lesions in other regions of the heart

(7) C lat 12 530 542 O t b 1955

tent When present they consist of lymphocytic infiltration *in the connective tissue muscular degeneration and increase* in collagen fibrils Clinically the syndrome is readily confused with coronary artery disease Response to ACTH radiation therapy and breathing exercises is prompt The cause is unknown and may be related to the shoulder hand syndrome

The syndrome has been encountered only in patients aged 30 75 most above 45 years It occurs commonly four to six weeks and occasionally several months after coronary occlusion When not related to coronary heart disease the history is usually negative It may be associated with angina pectoris causing persistent pain and giving the impression of status anginosus

The anterior chest wall syndrome is often misdiagnosed as coronary artery disease and treated accordingly The patients are convinced they have incurable heart disease and develop profound anxiety and depression The most important diagnostic features are tenderness of the anterior chest wall and the absence of signs and symptoms of progressive coronary artery disease Therapeutic tests with ACTH corticosteroids and x ray usually are diagnostic Two or three days of therapy relieve the pain and more prolonged treatment is usually curative Therapy usually does not exceed seven days If the symptom complex recurs therapy may be repeated

Chest pain after myocardial infarction is usually attributed to coronary insufficiency angina pectoris or anxiety neurosis However patients may have continual soreness of the anterior chest wall unaccompanied by signs or symptoms of coronary artery disease or pericarditis There is no associated thoracic oppression heaviness dyspnea and flatulence and the pain does not radiate General health is surprisingly good The pain does not respond to glyceryl trinitrate is continuous and is unrelated to heavy meals or exertion The vasomotor accompaniments of angina pectoris are absent and there are no systemic respiratory or cardiac symptoms No characteristic electrocardiographic changes can be detected except when S T and T changes are induced by anxiety

sions with 4 in the circumflex branch and 14 in the right coronary

Of the 59 infarcts 18 were healed and 41 were recent Two infarcts were found in the right ventricle of one heart but all others were in the left ventricle In only four instances was there occlusion of a main coronary without myocardial infarction and in each ca e the vessel had previously been occluded The area supplied by the artery had previously been infarcted Only four areas of infarction were found without complete occlusion of the corresponding main coronary artery In one the arterial narrowing was trivial one was associated with recent acute narrowing of a main coronary artery due to intimal hemorrhage and two healed infarcts were associated with severe long standing atheromatous narrowing of the corresponding arteries

The remaining 37 occlusions had caused 55 infarctions The additional 18 infarcts occurred in areas which could have been made ischemic by existing occlusions These extensions of infarct were not due to extension of the causative occlusion or to new occlusion but to necrosis of already ischemic muscle The infarcts were histologically of different ages and were recent in 16 instances When the infarct is completely healed the distinction of age is lost

In the area of infarction no arterial filling was seen until the third week after infarction had occurred By the eighth week all the infarcted areas had become revascularized The time required for revascularization probably depends on the adequacy of collateral channels and the size of the infarct

All 17 old occlusions had become recanalized Recanalized vessels in addition to the collateral vessel provide functional blood supply to an infarcted area In three cases further occlusions developed in the recanalized channel or adjacent to it resulting in a further infarct

Contrary to the findings of Blumgart Schlesinger and Davis obstruction of a main coronary artery almost inevitably leads to myocardial infarction Coronary occlusion without infarction is rare The discrepancy in part may have been due to failure by Blumgart and associate to identify all infarcts With the serial slice technic histologic examination of every suspected area whether or not changes are visible to the naked eye produces better correlation

cle damage in the left ventricle usually began in regions other than anterior

In only a third of the hearts was the infarct typically single anterior posterior or lateral These and a few hearts with multiple lesions of typical shape could be described by conventional methods but in over half the hearts the location and distribution of myocardial damage could not be described in these terms The best classification was based on size of infarct for single regional lesions and on age of infarct for those with multiple or widespread lesions To accurately classify a heart the ventricular myocardial lesions must be mapped which requires study of the anatomic location and coronary lesion

The myocardial lesions resulted from two degrees of disturbance of coronary perfusion In one group the usual anatomic arterial distribution was preserved even in badly damaged hearts In the other perfusion patterns were blurred or distorted because of multiple epicardial artery obstructions with well developed intramyocardial collateral circulation

Coronary Disease Pathologic Study is reported by P J D Snow A Morgan Jones and K S Daber[8] (Univ of Manchester) The hearts of 25 subjects with clinical coronary disease were perfused at autopsy by the Schlesinger technic with radiopaque mediums injected into the coronary arteries under pressure using different colors in the left and right arteries After a radiograph was taken as a guide the arteries were sectioned at 3-4 mm intervals and serial sections taken through the entire heart at 0 5 cm intervals All suspicious portions of the myocardium were examined histologically If no abnormality was found macroscopically sections were routinely taken from the anterior lateral and posterior walls of the left ventricle and the posterior wall of the right since infarcts are most common at these sites

Occlusions were found in 41 main vessels in these hearts and there were 59 infarcts in the myocardium Of the 41 occlusions 17 were old and all had recanalized 14 were recent without evidence of organization and 10 were intermediate in age and incompletely organized The anterior descending branch of the left coronary artery was the site of 23 occlu

(8) B t Heart J 27 503 510 October 1955

ished when peritrate® was taken after food and its use with the stomach empty was recommended

Of the four drugs only peritrate® was considered a long acting coronary vasodilator

Treatment of Angina Pectoris with a Nitroglycerin Ointment in 17 patients with severe angina unrelieved by other methods is reported by James A Davis and Bert H Wiesel[1] (Med College of Alabama) The ointment 2% nitroglycerin (nitrol®) was applied to the chest wall over an area 5 8 in in diameter The initial dose was ½ in of the ointment three or four times daily Each inch of ointment contains about 15 mg nitroglycerin

Definite benefit accrued when this treatment was used with other measures including rest and long acting nitrites sedatives and nitroglycerin sublingually Nine patients had good results and the number of nitroglycerin tablets required was markedly decreased Four patients were moderately improved subjectively and four were unimproved

A placebo was not substituted because of the possibility of inducing myocardial infarctions One patient had a second infarction while using the ointment he had noted a change in the effect of the ointment and had increased the amount from ½ to ¾ in This experience warns against a sudden discontinuance of the drug since coronary insufficiency might be suddenly increased with resulting myocardial infarction Test of the principle of slower absorption and prolonged action of an effective coronary vasodilator such as nitroglycerin ointment deserves further trial

• [Nitroglycerin ointment appears to be an effective long acting coronary dilator It is measured in inches as it is squeezed out of a tube The dose should be slightly less than that which produces a pounding headache in most patients a minimum of ½ in and a maximum of 2 in of the ointment. The effect appears to set in after about ½ hour and to last 3-4 hours The ointment may be applied over any cutaneous area and should be spread thinly but not rubbed It seems to be of special value in persons who are having frequent attacks at rest Those with nocturnal angina should apply it before going to sleep and if they continue to have attacks in the early morning hours should use an alarm clock to awaken them approximately four hours after the late evening application in order to apply it again in the middle of the night Sudden withdrawal of the ointment may result in a marked increase in anginal pain Therefore when the pain has been controlled by its use the dosage should be decreased very gradually by approximately 10% per week Since the use of the ointment may lead to marked tolerance to the effects of nitroglycerin it

(1) Am J M Sc 230 259 263 September 1955

There was no evidence that collateral circulation prevented myocardial infarction when a major coronary artery was occluded The area of infarction may have been limited or subsequent extension into adjacent ischemic zones may have been prevented by good collateral circulation As collateral circulation develops an infarct is less likely to extend but circulation cannot develop soon enough to prevent infarction when a major coronary artery is occluded

Long Acting Coronary Vasodilator Drugs Metamine® Paveril® Nitroglyn® and Peritrate® were evaluated by Henry I Russek Burton L Zohman Alice E Drumm William Weingarten and Virgil J Dorset[9] (New York) in 21 carefully selected patients with coronary artery disease These patients aged 46-69 had a constant positive ECG response to a given amount of exercise Nine had had a myocardial infarction and 15 had angina pectoris The response to exercise could be modified favorably with therapeutic sublingual doses of nitroglycerin before the test

Evaluation of vasodilator drugs by the relief of anginal pain is unreliable because pain is not a quantitative measure of the underlying coronary insufficiency and the element of subconscious bias on the part of both patient and physician cannot be eliminated

Metamine® (triethanolamine trinitrate biphosphate) 2-6 mg orally before breakfast had little or no effect on exercise response measured by the ECG Paveril® (dioxyline phosphate) 200 500 mg orally had a significant effect in only six patients but its action was not sustained and its influence never striking It was much less effective than papaverine® in comparable doses

Nitroglyn® (specially coated granules of nitroglycerine), in the usual dosage of 2 4 mg was totally inert In larger doses 4 8 and 9 6 mg it produced slight to moderate improvement for six hours in two thirds of the patients

Peritrate® (pentaerythritol tetranitrate in 10 20 mg doses had a marked effect in 14 of 21 patients It was as effective as nitroglycerin and its action after a latent period of 1 1½ hours could be demonstrated for 5-6 hours The clinical response was markedly attenuated or completely abol

(9) Circulation 12 169 175 August 1955

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(1) Am. J M S 230 259 263 September 1955

is not wise to continue it indefinitely Nitroglycerin ointment is useless in treatment of anginal attacks but in the experience of the editor is the most effective means of preventing such attacks—Ed.]

Ventricular Aneurysms of Heart Preliminary Report on Some New Clinical Signs Rustom Jal Vakil[2] (Bombay India) studied 20 proved cases of ventricular or parietal aneurysms

In 10 patients the apical impulse was very wide or diffuse and forcible and heaving It was seen and felt at the fourth left intercostal space halfway between the left parasternal and midclavicular lines Clinically the impulse appeared to be markedly displaced inwardly

In 13 patients in the recumbent position the up and down movement of the chest wall with each heartbeat was unusually slow or lagged particularly the downward movement This was termed myotonic impulse The cardiac impulse was abnormal in other ways 4 patients had reduplication of the impulse or a double thrust and 6 had a peculiar undulating or wavelike pulse particularly on palpation designated cardiac shudder or wavy impulse

In two patients the left costal margin had a heaving up and down movement synchronous with the heart beat It was best seen and felt with the patient supine and was associated with visible and palpable pulsation in the left hypochondrium and epigastrium and a relative craniad shift of the left costal margin

Nine patients had an impaired percussion note over the left side of the precordium comparable to that over serous effusions this was termed stony dulness In five a loud and long murmur—musical cooing or plaintive —occupied all of systole and early diastole it was best heard at the site of the cardiac impulse

• [Careful palpation of the precordium will reveal systolic bulges in a significant percentage of individuals with previous myocardial infarction. Patients with angina pectoris may display a palpable or visible bulge during the attack of pain with disappearance of the bulge as the pain subsides Those with infarction of the interventricular septum frequently display a systolic bulge just to the left of the sternum while those with infarction in the region of the apex may display bulges in that area.—Ed]

Postoperative Myocardial Infarction Report of 25 Cases Cardiac complications before during and after surgery par

( ) Am. Heart J 49 934-937 J n 1955

ticularly postoperative myocardial infarction are major hazards In a review of about 37 000 major and minor operations between 1948 and 1954 Fred Wasserman Samuel Bellet and Robert P Saichek[3] (Univ of Pennsylvania) found 25 cases of postoperative myocardial infarction an incidence of 0 07% 21 followed major and 4 minor procedures

Average age of patients was 64 0 years 10 were men Preoperative clinical evidence of heart disease was noted in 19 7 having hypertensive 6 arteriosclerotic 5 hypertensive and arteriosclerotic and 1 rheumatic heart disease General anesthesia was used in 21 spinal or local anesthesia in 2 each Surgery lasted an average of 1 hour and 50 minutes ranging from 30 minutes to 6 hours During surgery 12 patients had decrease in blood pressure of 40 or more systolic and 20 or more diastolic lasting 5 30 minutes and 6 others had insignificant hypotension

Myocardial infarction occurred in 23 during the day of or first week after surgery and in 2 during the second week Only eight had typical precordial pain with constriction four others had pain in the left shoulder right chest or mid epigastrium Hypotension was observed in 16 (64%) Five died three of the infarction and two of the infarction plus uremia and septicemia

No patient regardless of age should be denied urgent or emergency surgery Evaluating cardiac and renal function and giving intravenous therapy preoperatively may be life saving Before elective surgery detailed investigation is mandatory Cardiac enlargement hypertension previous myocardial infarction angina pectoris conduction disturbances and congestive heart failure increase risk of surgical myocardial infarction Anemia polycythemia infection and imbalances in hydration electrolytes and nutrition must be corrected

Preoperative medication in older patients should be limited to mildly depressive drugs More potent drugs may cause anoxia and sudden death Hypotension commonly caused by hemorrhage visceral manipulation and anesthesia must be avoided or immediately corrected The longer the period of shock the more probable myocardial infarc

(3) N w E gla d J M d. 25 967 974 J 9 1955

tion Oxygen inhalation should be continued postoperatively Muscle relaxant anesthetic agents (such as curare) have probably increased the anesthetic death rate

Postoperative myocardial infarction may be prevented if the preoperative status is optimal if the surgeon and anesthetist are alerted to the possibility of vascular complications and if hypotension arrhythmias and congestive heart failure are recognized and treated early Fluid blood and electrolyte balance must be carefully maintained When myocardial infarction occurs standard therapy should be employed and postoperative ambulation delayed two or three weeks

Significance of Serum Glutamic Oxalacetic Transaminase *Activity Following Acute Myocardial Infarction* is *reported* by John S LaDue and Felix Wroblewski[4] (New York) In normal individuals the level of serum glutamic oxalacetic transaminase is essentially the same from day to day and varies from 10 to 40 units/ml Levels above this were not found in patients with infectious neoplastic metabolic or degenerative diseases in whom acute destruction of heart skeletal muscle or liver tissue could be excluded but in 74 of 75 patients with transmural myocardial infarctions the transaminase activity was closely correlated with the clinical course and characteristic curves were obtained

Typically the level of transaminase activity was low for the first few hours after clinical onset of the infarction and rose to a peak in 12 24 hours In six days the level was usually normal again Five patients had extension of the original infarct and secondary rise in serum transaminase level Average level was 200 units on the first day of the infarction Two patients with 5 000 and 6 000 units on the second day had large infarctions at autopsy but both also had active liver disease

Transaminase levels were not elevated in other forms of heart disease except when associated with active myocardial damage The values were normal in patients with angina pectoris and coronary insufficiency even when associated with negative T wave changes of ischemia Shock heart failure cardiotonic drugs cortisone acute phlebitis and cerebrovascular damage did not affect the levels but acute

(4) Circulation 11 871 877 June 1955

myocardial damage acute liver injury skeletal muscle damage myositis including dermatomyositis and arterial occlusion all raised them However the curve of myocardial infarction does not resemble those of the other diseases

Serum glutamic oxalacetic transaminase rises precipitously after experimental carbon tetrachloride liver damage Liver cell injury in clinical carbon tetrachloride poisoning acute hepatitis and homologous serum hepatitis was associated with levels of 1 000 12 000 units These elevations persisted for a few days and moderate activity lasted for two or more weeks before returning to normal The curve does not resemble that of myocardial infarction

The height of the transaminase activity is roughly correlated to the size of the myocardial infarction The level of transaminase activity appears to be an index of heart muscle destruction but its role in diagnosis and management of heart disease requires further study

Present Status of Anticoagulant Therapy in Treatment of Myocardial Infarction Use and Misuse of Anticoagulants Evaluation of New Anticoagulants Their Indications and Dosage are discussed by Irving S Wright[5] (Cornell Univ) Unless contraindications exist all patients with myocardial infarction should receive anticoagulant therapy No physician can predict on the first day whether a patient will become worse on any day thereafter Anticoagulant therapy even in patients who remained in the good risk category reduced thromboembolic complications from 28 to 9/100 patients More comprehensive studies are needed of long term prophylactic use of anticoagulants after myocardial infarction and the trend is in that direction

Major methods of misuse of anticoagulant therapy are self medication without prothrombin tests for control prescribed medication without correct control administration despite contraindications withholding when therapy is indicated excessive dosage and inadequate dosage The most important contraindications are blood dyscrasias bleeding peptic ulcers recent brain surgery and inadequate laboratory services

The newer coumarin compounds are metabolized and act

(5) A I t M d 43 942 954 N mb 1955

at rates different from that of dicumarol® though the fundamental effect on prothrombin and factor VII is the same, and risk of bleeding is the same if not properly controlled. Average dosages are shown in the table. All the drugs and dosages must be controlled by prothrombin times.

Vitamin K_1 is very active when taken orally and 10-50 mg in orange juice or on food reduces prothrombin time within three to six hours. More than 50 mg is rarely advisable as the action is no more rapid and resistance to renewal of anticoagulants is increased.

AVERAGE DOSAGE SCHEDULE

COUMARIN DERIVATIVES	AVERAGE DOSES (CONTROLLED BY P. T.)		
	1st Dose	2d Dose	Following
Dicumarol®	300 mg	100 200	25 100
Tromexan®	1 500	900	300 900
Cumopyran®	150	75	50 75
Marcumar	21	9	3
Warfarin sodium	50 75	25 37 5*	
Phenylindandione	150	50-75	25 75
Dipaxin®	18	9	3 6

* Administered at 3 day intervals

Heparin is the only drug of its type suitable for clinical use. Paritol® and treburon® frequently produce shock, urticaria and alopecia and have been abandoned. Phosphorylated hesperidin is still experimental. Trypsin and plasmin are not recommended for general use until further evaluation.

Evaluation of Effect of Continuous Long Term Anticoagulant Therapy on Prognosis of Myocardial Infarction. Report of 82 Cases was made by M. M. Suzman, H. D. Ruskin and B. Goldberg[6] (Johannesburg). A control group of 88 patients received anticoagulants only during the acute phase of infarction. Most patients received heparin during the acute phase and after the first week were maintained on an oral anticoagulant, usually dicumarol.® The short term treatment ranged from 3 weeks to 3 months and the long term therapy from 3 to 76 months. Prothrombin control was maintained at twice normal prothrombin times by testing at weekly or two week intervals.

The patients were drawn from unselected hospital admis-

(6) Circulation 12 338 35 September 1955

sions and private practice After recovery from the acute phase the patient decided whether he would continue on anticoagulant therapy The only requisites were regular attendance at the clinic and laboratory Those whose previous episodes and presenting attacks of infarction were more severe tended to accept the regimen readily Patients who declined or were unable to undertake the continuous treatment constituted the control group and were followed for comparable periods

The two groups did not differ significantly in age sex or previous angina pectoris Previous myocardial infarction was more common in the long term group and a significant difference in the total incidence of previous coronary artery disease weighed against these patients The presenting attack tended to be more severe in the patients who elected to continue anticoagulant therapy

In the 82 patients in the long term group the mortality rate was 7 3% and 7 patients had recurrent infarctions while under treatment In the 88 patients in the short term group the mortality rate was 33% and 24 patients had recurrent myocardial infarctions If only the severe cases of infarction are considered of the 67 patients treated for a long period 7 had recurrent infarctions and the mortality rate was 9% In the short term group 60 patients had severe infarctions 21 had recurrences and the mortality rate was 46 7%

In the severe cases with a history of previous infarction the mortality rate in the long term group (21 cases) was 14 3% compared to 66 6% in the short term group (15 cases)

During the course of the study cardiac failure occurred with similar frequency in both groups but the mortality associated with this complication was 11 8% in the long term compared to 57 1% in the short term group The incidence of angina after the presenting attack of myocardial infarction was approximately the same in both groups Angina was improved or relieved in 56% of the long term group and in 23% of the short term group

Hemorrhage occurred in 12 patients hematuria in 9 and epistaxis melena and hemarthrosis in 1 each Two patients died of hemorrhage One had a cerebral hemorrhage while

at rates different from that of dicumarol® though the fundamental effect on prothrombin and factor VII is the same and risk of bleeding is the same if not properly controlled Average dosages are shown in the table All the drugs and dosages must be controlled by prothrombin times

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Marcumar	21	9	3
Warfarin sodium	50 75	25 37 5*	
Phenylindandione	150	50 75	25 75
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(6) Circulation 12 338 352 September 1955

the heparin group there were five nonfatal recurrences (three acute myocardial infarctions and two minor cerebral episodes)

For reasons of safety blind study technics were not used but patients observations were of interest Symptoms decreased on placebo in 25 35% of the control group but favorable response gradually decreased in some patients Symptomatic improvement occurred in 50 75% of patients who received heparin and was usually fairly well maintained Most often in contrast to placebo patients there was slowly progressive improvement for several months in the heparin group

In patients receiving heparin there were only three instances of major hemorrhage two intestinal and one renal X rays revealed adenocarcinoma of the stomach in one and a kidney stone in another In the one patient in whom hemorrhage was apparently due to heparin itself the drug was discontinued There were no fatalities from hemorrhage Of six minor bleeding episodes one was nasal four rectal and one pulmonary All patients with rectal bleeding had had previous hemorrhoidal bleeding and the patient with bloody sputum had known bronchiectasis There were two instances of post traumatic minor hemorrhage and three of large painful hematomas at the site of injection Heparin therapy was stopped in only four cases because of complications No hemorrhage occurred in six patients with known chronic duodenal ulcers antacid therapy was maintained in all Hypertension apparently added little danger to heparin therapy When surgery was necessary no heparin was given in the 48 hours before operation and no increased bleeding was noted No cardiovascular complications occurred after five major surgical procedures in the heparin group there was one nonfatal myocardial infarction after six major operations among controls

There is apparently very little tendency in dosages used for a cumulative heparin effect sufficient to result in maintained therapeutic anticoagulation Thus clotting time determinations are superfluous in patients without severe liver disease

• [There is strong evidence that heparin has an effect on blood lipids entirely aside from its effect on coagulation It appears unlikely that

the prothrombin time was twice normal He was known to be hypertensive and dicumarol® was considered noncontributory The other in severe congestive failure was in poor prothrombin control and had massive intestinal hemorrhage The bleeding was stopped and anemia corrected with vitamin K and blood transfusions but he died in congestive cardiac failure Dicumarol® was considered an indirect contributory cause of death Long term therapy was discontinued by 38 patients not included in this study Fifteen stopped because of hemorrhagic manifestations but the bleeding was not severe enough in any to have warranted permanent discontinuation of anticoagulants

Patients in whom the presenting myocardial infarction is mild and is the first attack and who receive short term anticoagulant therapy have a favorable prognosis concerning subsequent infarction cardiac failure and death irrespective of whether anticoagulants are indefinitely continued The patients most likely to benefit from long term anticoagulant therapy are those in whom the presenting myocardial infarction is severe and previous myocardial infarctions have occurred

• [The study appears to be well controlled and the results constitute impressive evidence for the value of long term anticoagulant therapy All of the investigations of this type emphasize the absolute necessity of proper control of prothrombin time in patients treated in this manner —Ed]

Controlled Study of Effect of Intermittent Heparin Therapy on Course of Human Coronary Atherosclerosis is reported by H Engelberg R Kuhn and M Steinman[7] (Cedars of Lebanon Hosp Los Angeles) Heparin 200 mg subcutaneously was administered twice weekly to 105 patients with known previous myocardial infarction A comparable group of 117 persons received saline placebos There were four deaths due to cardiovascular disease among the 105 patients (average age 62 6) who had 2 067 months (range 2 27) of heparin therapy In the control group (average age 61 7) who had 2 183 months (range 1½ 25½) of placebo therapy there were 21 deaths from cardiovascular disease a statistically significant difference ($p < 0.01$) In this group there were also 18 nonfatal recurrences (14 myocardial infarctions 3 cerebral episodes and 1 leg amputation for gangrene) In

(7) Circulation 13 489-498 April 1956

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the beneficial results reported in this study could have been due to the effects on blood coagulation. The relative advantages of long term heparin therapy versus long term dicumarol® therapy in adequate dosage remain to be evaluated —Ed]

Should the Patient with a Healed Myocardial Infarction Avoid Physical Exertion? Weldon J Walker[8] (Baylor Univ) believes that physical exertion does not precipitate myocardial infarction and that restriction of activity in a patient with a healed infarction who has no residual cardiac or coronary insufficiency probably shortens actual survival and certainly shortens useful life

Coronary atherosclerosis is practically a universal condition among American men It has been demonstrated in 77% of United States soldiers killed in Korea at an average age of 22 1 years and is even more frequent in older men Life expectancy after myocardial infarction is better than formerly believed A recent insurance study showed that in the 40 60 age group half lived more than 10 years after coronary occlusion

If physical exertion is dangerous for patients with coronary atherosclerosis all American men should retire today since most have this disease However most evidence indicates that physical activity protects against atherosclerosis British workers have found that men in heavy work had an over all mortality rate from coronary heart disease less than half that of men doing light work and that early mortality rates were lower and survival time from onset of disease longer in the former Master and Jaffe in a study of onset of 1 347 attacks of coronary occlusion found that attacks were evenly distributed through all hours of the day and night and onset of less than 2% was associated with unusual exertion (probably coincidental) In the Armed Forces the highest incidence of myocardial infarction has been found in the sedentary branches If exertion is important in precipitating coronary occlusion the highest incidence should be in the more strenuous branches of the services and among laborers

Exertion and emotion are important in precipitating angina Patients are advised to avoid activity that will cause pain since the associated ischemia may induce dangerous ar

(8) J Am Geriatrics Soc 3 959 963 December 1955

rhythmias Below pain level activity probably stimulates collateral circulation and prevents thrombosis

Strict bed rest during the acute stages of myocardial infarction minimizes the possibility of myocardial rupture ventricular aneurysm or congestive failure After the first month cardiac rupture is no longer a threat and the healed area is least likely of all the myocardium to rupture Thereafter activity should be unrestricted unless the patient has dyspnea angina or arrhythmia on exertion

The patient must understand that further infarctions cannot be prevented by limiting activity and that death is no more likely while working than at rest Restriction may result in loss of many years of useful living since 75% of patients can return to productive employment An unfounded fear of death from work causes needless invalidism

Role of Diet and Hormones in Prevention of Myocardial Infarction is reviewed by Louis N Katz[9] (Michael Reese Hosp) Atherosclerosis is a distinct entity among the arterioscleroses It is a disease no longer dogmatically identified with aging associated with altered cholesterol lipid lipoprotein metabolism Incidence varies significantly among different peoples but the differences cannot be attributed exclusively to race nationality genetic constitution climate or geography One factor possibly conditioning the variable incidence of hypertension and perhaps atherosclerosis may be the general life situation—its pace stress and influence on temperament diet plays a decisive role

Atherosclerosis is not prevalent in races consuming a high protein diet (naturally low in cholesterol and neutral fat) and plasma cholesterol levels are remarkably low Populations ingesting over the life span a diet rich in cholesterol lipid manifest a tendency for plasma cholesterol levels to rise postnatally remain elevated in the early decades and rise further in the later decades Mortality and morbidity due to atherosclerosis in these populations are extensive When such groups are compelled to abandon dietary habits for a significant period the tendency to atherosclerosis is reversed and the trend of plasma cholesterol levels is downward Ingestion over the years of a diet rich in cholesterol

(9) A n. I t. M d. 43 930 941 Novembe 1955

lipid is prerequisite to development of significant atherosclerosis in a population Once the prerequisite diet has been ingested individual differences hereditary constitutional etc determine whether atherosclerosis develops

Atherosclerosis has now been successfully induced in practically every laboratory animal species by altering cholesterol lipid lipoprotein metabolism and effecting hypercholesterolemia through diet alone or combined with changes in endogenous metabolism In chicks a potentially atherogenic diet was significantly reversed by chronic undernutrition withdrawal of neutral fat addition of excessive neutral fat supplemental plant sterols or a defatted brain extract In contrast numerous so called lipotropic factors—choline inositol pancreatin activated whole pancreas antifatty liver factor tocopherols vitamin B_{12} lipocaic etc —were without influence on hypercholesterolemia and atherosclerosis in cholesterol fed intact or depancreatized chicks These negative results are in complete agreement with those reported in other laboratory animals and in man There is no justification for the widely advertised claims that proprietary lipotropic factor preparations can prevent or benefit atherosclerosis in man

The most striking results in studies on hormones and atherosclerosis have been obtained with estrogens In cholesterol fed cockerels estrogens induced feminization increased ratio of free to total cholesterol levels in the plasma increased hyperphospholipemia decreased ratio of total cholesterol to lipid phosphorus levels in the plasma depressed alpha lipoprotein and reduced beta lipoproteins in the S_f 20-100 range levels and prevented coronary atherogenesis without influencing the formation of aortic lesions All estrogenically active compounds were effective but several estrogen like compounds of low feminizing potency did not influence lipid patterns and coronary atherogenesis Progesterone was without influence Estrogens reversed both the lipophage and fibroblastic components of coronary atherosclerotic plaques

Considerable data from studies in man also suggest that physiologic estrogen secretion in the female may exert significant antiatherogenic influence A long term clinical study has been begun to assess the effect of estrogens in

preventing recurrences of myocardial infarction and prolonging life in men under 50 with recent proved myocardial infarction Preliminary results are encouraging and a definite answer should be available in three to five years

Effects of Restriction of Dietary Fat and Cholesterol on Serum Lipids and Lipoproteins in Patients with Hypertension were studied by Frederick T Hatch Liese L Abell and Forrest E Kendall[1] (Columbia Univ) Most patients had initial resting blood pressure greater than 200/120 mm Hg and impaired function of the eyes brain heart or kidneys

During a control period of 4 18 weeks the patients received a salt poor hospital diet containing about 2 5 Gm sodium chloride and 85 Gm fat daily No appreciable difference existed between the patients and a comparable group of normal subjects The average levels of free and esterified cholesterol lipid phosphorus and serum lipids were unchanged The average serum neutral fat level was significantly higher in the patients with hypertension

After the control diet 44 patients remained for 4 20 weeks on an unmodified Kempner rice diet containing about 0.25 Gm salt and 3 Gm fat with 30 Gm protein daily The only statistically significant change was a 15% decrease in serum total cholesterol level

Ten patients remained on a special rice diet with added protein carbohydrate powder which contained 0 25 Gm salt 40 80 Gm protein and 20-40 Gm fat daily Another 10 patients received the same diet except that fat was increased to 55 Gm and protein to 90 Gm daily

No significant changes in patterns of serum lipid levels were produced by adding 0 5 to 3 Gm sodium chloride per day to the low sodium diets or by raising the protein content to 40 80 Gm daily Partial or nearly complete restriction of dietary fat and cholesterol did not reduce serum lipid and lipoprotein levels below normal in any patient

Compensatory metabolic mechanisms must exist for maintaining the serum lipid and lipoprotein concentrations Carbohydrate and protein appear to be sources of endogenous lipid synthesis Drastic restriction of fat and cholesterol produced variable lipid patterns Serum cholesterol ester levels

(1) Am J Med 19 48 60 J ly 1955

usually decreased with daily fat intakes below 40 Gm Free cholesterol and lipid phosphorus concentrations were inconsistently changed About a fifth of the patients had neutral fat lipemia Diet did not significantly alter the concentration of the S_f 12 20 particles but substantial increases in S_f 20-100 were provoked by the rice diet

The response of serum lipid and lipoprotein levels to restriction of dietary fat was not predictable for any given patient The changes could not be correlated with severity of hypertension or with presence or absence of arteriosclerotic complications The decrease in serum cholesterol levels was due to fat, rather than cholesterol restriction

Effect of Sitosterol Administration on Serum Cholesterol Level and Lipoprotein Pattern Claude Joyner Jr and Peter T Kuo[2] (Univ of Pennsylvania) treated seven cardiac patients—four women age 39 50 and three men 34-62 Five had serum cholesterol levels below 300 mg /100 cc one patient just over 300 mg All were on a full normal diet and none knew why the sitosterol was given The preparation was a 13% suspension of beta sitosterol derived from tall oil Two of the patients were also given a powder containing 85% beta sitosterol from tall oil

The sitosterol reduced the serum cholesterol regardless of the initial cholesterol level although the patients remained on an unrestricted diet No untoward side effects were noted and no patient s weight changed significantly The minimal effective dose was above 10 Gm daily for a four week course of treatment In two patients on a strict low fat diet sitosterol further reduced the serum cholesterol When the cholesterol concentration was significantly reduced the electrophoretic lipoprotein pattern showed a decrease in the large beta lipid zone including the tall beta peak without significant change in the alpha lipid fraction or in the protein pattern

Experimental and clinical data indicate an increase in atherosclerosis in hypercholesteremia and lipoprotein abnormalities Atherogenesis may possibly be regarded by correcting lipid abnormalities A low fat diet will reduce the serum cholesterol but is inconvenient and difficult to enforce over

( ) Am J M S 230 637 647 Dec mbe 1955

long periods Without dietary restriction sitosterol may reduce the serum cholesterol

Effects of Sitosterol on Serum Lipids were evaluated in 14 patients for an average of 40 weeks by Maurice M Best Charles H Duncan Edward J Van Loon and Joan D Wathen[3] (Louisville Ky) None of the patients had hypothyroidism diabetes mellitus or nephrosis 12 had elevated serum cholesterol levels and 2 were normal volunteers Immediately before inge tion of food 6 8 Gm beta sitosterol was given orally the total daily dose being 20 25 Gm or occasionally 50 Gm Each patient received a placebo for one or more periods Diet was unrestricted No toxic or adverse side effects were noted

During each period of sitosterol administration serum cholesterol and total lipid values decreased significantly below mean control values During placebo and control periods levels returned to pretreatment range The lipid phosphorus level was not consistently changed but in most patients the neutral fat level decreased during sitosterol administration

Serum cholesterol level fell after the first week of beta sitosterol treatment and declined further during the succeeding everal weeks The lower serum cholesterol level was maintained throughout the period of administration with no tendency to escape Reduction in serum total lipid level was similar to that of cholesterol and was also sustained during therapy but lipid phosphorus level varied both during treatment and control periods

The higher the control level of cholesterol the greater the fall during sitosterol therapy the fall ranging from 6 5 to 28 8% The 12 patients with hypercholesterolemia had a mean fall of 16% whereas the 2 normal subjects had an average decrease of only 6 8% In seven patients serum lipoprotein level tended to be lower in the S_f 3 100 class during administration of sitosterol but the effect was not consistent

The effects of sitosterol were attributed to interference with cholesterol absorption Sitosterol probably competes for esterification a step in the transport mechanism by which cholesterol is absorbed Dietary restriction alone does

(3) Am J M d 19 61 70 J ly 1955

not produce identical results for sitosterol reduces absorption of cholesterol from both bile and diet

The changes in serum lipid and lipoprotein levels during sitosterol administration were in the direction considered desirable in atherosclerosis *Further study in man is indicated*

• [At the present time it would appear that there are three methods of reducing serum cholesterol One of these is *rigid restriction of fat* in the diet The evidence that there is a strong correlation between the percentage of fat consumed and the incidence of coronary artery disease is impressive A second method is the use of estrogens Whether it is going to be possible to reduce serum cholesterol in males and in postmenopausal females by the use of estrogens that do not cause untoward effects remains to be determined The third method is attempting to block cholesterol absorption from the intestinal tract by the use of sitosterol or of some related substance On theoretical grounds the latter method has a distinct advantage over cholesterol restriction and over fat restriction It should be remembered that a very considerable portion of the circulating cholesterol is formed in the body This is excreted in the bile and reabsorbed from the intestine The advantage of using an agent that *blocks cholesterol absorption would appear to be that it acts not only* on ingested cholesterol but also on endogenous cholesterol Obviously long range studies over several years on a large number of patients are needed In the meantime the approach to the problem by blocking cholesterol absorption from the intestine is exciting and encouraging —Ed]

√*Prevention of Shoulder Hand Syndrome* The syndrome occurs in a variety of diseases occasionally without apparent cause but oftenest after myocardial infarction or in patients with severe angina pectoris It is equally common in both sexes

Pain may start between eight days and seven months after myocardial infarction during convalescence usually in the left shoulder and hand The shoulder pain is thought to perpetuate a reflex nerve disturbance that leads to periarthritis of the shoulder with pain tenderness and crepitus The hand and fingers swell and motion in the shoulder and hand is limited Local ischemia due to vasoconstriction is also induced which may cause fibrous thickening and contractions *in the palmar fascia (Dupuytren s contracture)* Inactivity and ischemia account for atrophy of muscles in the affected limb and *for osteoporosis*

Kurt George Leichtentritt[4] (New York) prohibited inactivity of both *shoulders and hands from onset of myocardial* infarction even while the patient was in acute shock and receiving oxygen Daily the arms of the patient were *passively* slowly and gently raised one at a time straight up and paral

(4) GP 12 108 109 S pt mbe 1955

lel to the body as high above the head as condition and tol erance permitted *About 14 days after onset of myocardial* infarction the patient began these movements actively two or three times a day and continued this daily exercise indefi nitely

Of 71 patients with myocardial infarction between 1944 and 1949 not given this treatment 13 (18%) had the shoul der hand syndrome Of 93 patients with myocardial infarc tion between 1949 and 1954 treated by this method none had the syndrome Daily arm exercises have also been prescribed for patients with frequent and severe angina pectoris with equal success

• [There are a few patients in whom the shoulder hand syndrome devel ops before the appearance of overt manifestations of coronary artery disease Most of them will develop typical anginal pain on moderate to severe physical exertion or will display significant electrocardiographic changes with such exertion Therefore middle aged ind viduals and more particularly males with this syndro ne should be studied with care for evidence of angina —Ed]

ARRHYTHMIAS

Mechanism of A V Arrhythmias With Electronic Ana logue of Human A V Node is described by Robert P Grant[5] (Nat l Inst of Health) Atrioventricular arrhythmias exist when activation of the ventricles by the atria is disturbed e g prolonged P R interval Wenckebach s phenomenon A V dissociation nodal and reciprocal rhythms and incom plete and complete heart block

The A V rhythm disturbance of acute rheumatic fever is unique Although prolonged P R intervals Wenckebach pe riods and A V dissociation are common complete and in complete heart blocks are rare This indicates that conduc tion delay cannot be a prominent part of the mechanism The fact that a patient with P R prolongation due to acute rheu matic fever can develop A V dissociation or Wenckebach pe riods by coughing breath holding or being passively tilted and returned to horizontal position suggests that a single defect is responsible for all these phenomena When the de fect is stable P R prolongation is produced and when un

(5) Am J M d 20 334 344 M h 1956

stable the other two arrhythmias The specific and constant time characteristics of the P R interval in Wenckebach periods and A V dissociation resemble the harmonics of two unstable coupled electronic oscillators

The A V arrhythmia of acute rheumatic fever is a functional rather than a structural alteration in the A V node because it is uniformly corrected by atropinization intravenously This is not a manifestation of central vagal activity Enhanced nodal rhythmicity is probably a basic abnormality in the disturbed conduction of acute rheumatic fever Besides *the threshhold of the A V node is probably* elevated Under these circumstances when the P rate and the nodal rate become coupled as two oscillators tend to pull in fixed P R prolongation is produced When the two oscillators pull apart Wenckebach periods or A V dissociation are produced The precise exponential nature of the P R interval growth in Wenkebach s phenomenon is strong evidence that the arrhythmia is related to some form of harmonic or resonant electric behavior such as is produced by coupled oscillators

Previous hypotheses of the mechanism of Wenckebach s phenomenon do not explain the observed facts The precise progressive lengthening of the P R interval by an exponentially dwindling amount is not explained by a simple increase in relative refractoriness within the A V node

The lengths of the P R intervals in the Wenckebach period are unrelated to the degree of P R prolongation which preceded it It is inaccurate to call Wenckebach periods second degree heart block and fixed P R prolongation first degree heart block They probably reflect different manifestations of the same abnormality rather than different degrees of A V conduction

Precipitation of Ventricular Arrhythmias Due to Digitalis by Carbohydrate Administration orally or intravenously was found in 7 of 37 heart patients studied by Ernest Page[6] (Med College of Alabama) Ventricular arrhythmias appeared on 10 occasions after 100 Gm glucose by mouth 3 times after a high carbohydrate meal once after 50 cc of 50% gl[illegible] intravenously and once after slow intravenous infu[illegible] glucose In one patient the same changes

6 176 A gu t 1955

were induced by glucose intravenously as by a high carbohydrate meal in another the same changes occurred after glucose orally as after a high carbohydrate meal

At the time of the test five of the seven patients had nausea or ventricular arrhythmias and were considered to have digitalis toxicity two were not clinically toxic In 3 of the 30 in whom arrhythmias were not induced digitalis intoxication was suspected clinically Of the seven with positive reactions three had been receiving potassium chloride by mouth 6 Gm or more daily but none for at least eight hours before the test

Fatal ventricular arrhythmia is a hazard of digitalis therapy and usually is preceded by ventricular extrasystoles Certain precautionary measures may be advisable especially in the patient digitalized to a critical point The prophylactic administration of potassium salts with carbohydrates orally or intravenously and the avoidance of excessive blood sugar fluctuations excessive emotional discharges or spontaneous hypoglycemia may be indicated

In the seven patients near digitalis toxicity carbohydrate given orally or intravenously precipitated ventricular premature beats in six and ventricular tachycardia in one This effect was attributed to reduction in the arterial plasma potassium level by the carbohydrate

• [Parenteral or oral administration of carbohydrate lowers plasma potassium In a patient on the verge of overt digitalis intoxication such a hypokalemia may precipitate manifestations of digitalis intoxication. Therefore when one is in doubt as to whether a patient has had too little or too much digitalis administration of a high carbohydrate meal or of 25 Gm. glucose intravenously with ECGs at intervals during the next 90 minutes is likely to settle the question If the patient is on the verge of digitalis intoxication frequent premature beats may be precipitated Should ventricular tachycardia result, potassium salts should be given immediately

This investigation would appear to suggest that patients who are receiving digitalis in high dosage should be given not only potassium salts but also a high protein low carbohydrate diet.—Ed]

Effect of Molar Sodium Lactate in Increasing Cardiac Rhythmicity Its Use in Treatment of Slow Heart Rates Stokes Adams Syndrome and Episodes of Cardiac Arrest A clinical and experimental study is reported by Samuel Bellet Fred Wasserman and Jerome I Brody[7] (Philadelphia) The infusion was given intravenously to all patients except five

(7) T A Am Phy 68 161 176 1955

stable the other two arrhythmias The specific and constant time characteristics of the P R interval in Wenckebach periods and A V dissociation resemble the harmonics of two unstable coupled electronic oscillators

The A V arrhythmia of acute rheumatic fever is a functional rather than a structural alteration in the A V node because it is uniformly corrected by atropinization intravenously This is not a manifestation of central vagal activity Enhanced nodal rhythmicity is probably a basic abnormality in the disturbed conduction of acute rheumatic fever Besides the threshhold of the A V node is probably elevated Under these circumstances when the P rate and the nodal rate become coupled as two oscillators tend to pull in fixed P R prolongation is produced When the two oscillators pull apart Wenckebach periods or A V dissociation are produced The precise exponential nature of the P R interval growth in Wenkebach s phenomenon is strong evidence that the arrhythmia is related to some form of harmonic or resonant electric behavior such as is produced by coupled oscillators

Previous hypotheses of the mechanism of Wenckebach s phenomenon do not explain the observed facts The precise progressive lengthening of the P R interval by an exponentially dwindling amount is not explained by a simple increase in relative refractoriness within the A V node

The lengths of the P R intervals in the Wenckebach period are unrelated to the degree of P R prolongation which preceded it It is inaccurate to call Wenckebach periods second degree heart block and fixed P R prolongation first degree heart block They probably reflect different manifestations of the same abnormality rather than different degrees of A V conduction

Precipitation of Ventricular Arrhythmias Due to Digitalis by Carbohydrate Administration orally or intravenously was found in 7 of 37 heart patients studied by Ernest Page[6] (Med College of Alabama) Ventricular arrhythmias appeared on 10 occasions after 100 Gm glucose by mouth 3 times after a high carbohydrate meal once after 50 cc of 50% glucose intravenously and once after slow intravenous infusion of 10% glucose In one patient the same changes

(6) Am J Med 19 169 176 August 1955

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(7) T A Am Phy s 68 161 176 1955

who received it by intracardiac injection during the terminal portion of life The dose varied considerably Normal persons received 100 250 cc over 10 20 minutes patients with myocardial damage 100 160 cc and patients with cardiac arrest from 17 cc in 30 seconds to 500 cc over 4 5 hours One subject received 900 cc over six hours

In three patients with sinus bradycardia (with a control ventricular rate of 30-40/minute) the rate increased by 50 75% In five of six patients with partial A V heart block the rates rose from 32 to 45 35 to 49 38 to 50 44 to 88 and 50 to 80/minute The sixth patient with a normal rate of 88 was unaffected by the infusion

In four patients with complete heart block the ventricular rate increased from 71 to 107 40 to 50 42 to 47 and 32 to 45 with comparable increases in auricular rate In three others who also had hyperpotassemia the ventricular rate increased from 15 to 100 26 to 71 and 30 to 52 after the infusion In three patients with complete A V block and auricular fibrillation ventricular rates increased from 32 to 38 39 to 48 and 45 to 52 Two patients had no significant change in auricular or ventricular rates

The blood pressure in normal subjects given 100 200 cc was not significantly altered nor was any change noted in patients with partial or complete A V heart block In patients in shock with a slow ventricular rate blood pressure tended to return to normal as the rate increased Similar effects were noted in three patients resuscitated from Stokes Adams seizures and in two patients in terminal cardiac arrest

Molar sodium lactate was given to four patients with Stokes Adams attacks In one the heart beat was restored during 10 separate episodes he died during the last episode for which he did not receive this treatment Cardiac beating was restored in the two patients who also had complete A V block The dose in one was 80 cc in several minutes In the other repeated injections of 40 60 cc consistently restored ventricular beating in each of multiple episodes In the fourth patient the period of asystole lasted over six minutes and although ventricular beating was restored the patient did not recover

In treatment of Stokes Adams attacks molar sodium lac

tate should be given as soon after the attack as possible pref erably within a minute or two Recovery after longer stand still is less likely During an attack 20 80 cc should be given rapidly intravenously by syringe in ½ 2 minutes Intra venous drip should then be started and the patient monitored by continuous ECG control Continuous administration of 15 20 drops/minute may prevent further seizures if they tend to recur Faster rate of infusion may be required by some patients Other methods of resuscitation including ar tificial respiration and oxygen should be used to prevent cerebral anoxia The infusion does not permanently increase heart rate the ventricular rate decreasing to control levels *two to three hours after infusion is stopped*

Conspicuous improvement in the ECG was noted in most of 12 patients with terminal cardiac arrest If administered within 30 120 seconds of onset molar sodium lactate induced return to more normal configuration of the QRS complex and increased heart rate and blood pressure

No serious metabolic abnormalities are induced by the treatment For several hours after infusion a base bicarbon ate type alkalosis exists with commensurate increased pH Within two to three hours more than half the injected so dium is excreted

External Electric Stimulation of Heart in Cardiac Arrest Stokes Adams Disease Reflex Vagal Standstill Drug In duced Standstill and Unexpected Circulatory Arrest were treated by Paul M Zoll Arthur J Linenthal Leona R Nor man Milton H Paul and William Gibson[8] (Harvard Med School) Stokes Adams attacks are due to cerebral ischemia during slow idioventricular rhythm ventricular standstill ventricular tachycardia or ventricular fibrillation They pre sent as dizziness syncope prolonged unconsciousness or convulsions and may end in death Attacks may be frequent and severe but if the patient survives them he may live many years

A new approach to Stokes Adams disease and to reflex vagal standstill standstill due to drug toxicity and unex plained circulatory arrest in the operating room is an exter nally applied cardiac pacemaker to stimulate the heart elec

(8) A M A A b I t M d 96 639-653 N mbe 1955

trically Effective ventricular contractions are produced for long periods The cardiac pacemaker produces purely mono phasic rounded electric impulses with an average duration of 2 3 msec Voltage output and rate of impulse formation can be varied The effective stimuli in the authors patients ranged from 50 to 200 ma and from 20 to 100 volts The pacemaker is attached to the patient by circular chest elec trodes 3 cm in diameter placed on the left anterior chest one at V_5 and one at V_3

Of 37 patients with recent Stokes Adams attacks 25 were resuscitated from ventricular standstill by the external car diac pacemaker on repeated occasions and adequate circula tion was maintained for as long as five days until an endog enous pacemaker was again able to function Ten of these patients were living 1 24 months after resuscitation Fre quent recurrence of attacks was striking in four patients de spite intensive drug therapy and continuous stimulation was repeatedly necessary The other 12 patients had no re currences

The three major therapeutic problems in Stokes Adams disease are emergency resuscitation from a major attack ter mination of persistent ventricular standstill and prevention Emergency resuscitation must be prompt because cerebral and coronary circulation must be restored within three or four minutes Though ECG identification of the mechanism is useful treatment must be begun even if an ECG is not available Forceful slapping of the precordium cardiac punc ture with lateral tapping of the needle and intracardiac in jection of 0 1 0 5 ml of 1 1000 solution of epinephrine hydro chloride should be tried in sequence while awaiting the elec tric pacemaker These measures are simple and immediately available but are often ineffective and sometimes cause fatal complications The electric pacemaker is completely safe and uniformly effective in treating slow ventricular rates or standstill It should be attached to the patient as soon as po sible and stimuli of increasing intensity applied until cardiac responses occur Stimulation may be stopped if adequate spontaneous ventricular activity appears but the external pacemaker should remain attached and the patient closely observed for at least a month An instrument that monitor

electric activity from the heart and sounds an alarm when ventricular standstill occurs is available

Persistent ventricular standstill may occasionally be effectively treated with constant intravenous infusion of 4 16 μg epinephrine/minute Isuprel® and levophed® also can arouse idioventricular pacemakers but apparently excite multifocal ventricular activity more readily than does epinephrine

Ephedrine and epinephrine are most useful in preventing frequent Stokes Adams attacks Ephedrine sulfate is usually started with 0 025 Gm three or four times daily by mouth and increased to 0 06 Gm or more if necessary until attacks no longer occur or until toxicity is observed It may also be given intramuscularly Epinephrine hydrochloride is usually given subcutaneously 0 3 0 5 ml of 1 1000 solution at one to four hour intervals The value of atropine isuprel® and paredrine® in preventing attacks has not been established Vagolytic and sympathomimetic drugs digitalis nitrites and ACTH have been used but their effects are inconsistent

External cardiac stimulation successfully terminated ventricular standstill due to digitalis or procaine amide in four patients and that due to reflex vagal stimulation in three In five patients with unexpected circulatory arrest the external pacemaker successfully resuscitated the heart In seven others it was ineffective because the arrest was due to ventricular fibrillation or because treatment was delayed until anoxia made the myocardium unresponsive The electric pacemaker must be applied promptly before resorting to thoracotomy and cardiac massage

Major untoward effects of the electric pacemaker were chest pain and muscular twitch usually made tolerable by demerol® or paraldehyde If the electrodes are placed too low normal diaphragmatic movement may be impaired No evidence was found of damage to the heart or neighboring structures from the electric current In patients treated more than one day superficial ulcerations appeared under the electrode They may be avoided by frequent small changes in electrode position and meticulous care of the skin

Treatment of Unexpected Cardiac Arrest by External Electric Stimulation of Heart Cardiac arrest may occur unexpectedly during various diagnostic and therapeutic pro

cedures particularly under anesthesia The usual cause is ventricular standstill Thoracotomy and cardiac massage are hazardous and the rate of recovery is only about one in three Paul M Zoll Arthur J Linenthal Leona R Norman Milton H Paul and William Gibson[9] (Harvard Med School) successfully resuscitated the heart from ventricular standstill in eight patients with an external electric pacemaker Thoracotomy and cardiac massage were unnecessary The arrest occurred during surgery in seven patients and during pericardiocentesis in one Five recovered completely two died during surgery and one died eight hours after operation

In nine other patients in whom unexpected cardiac arrest developed during various procedures (jugular puncture intravenous pyelography bronchography cardiac catheterization endotracheal intubation hip nailing cholecystectomy and cardiac surgery) stimulation with the cardiac pacemaker was unsuccessful In two the circulatory arrest was due to ventricular fibrillation and in the other seven electric stimulation was delayed more than five minutes after arrest had occurred The responsiveness of the heart diminishes progressively with continued anoxia and effective ventricular contractions must be resumed within three minutes to avoid cerebral and cardiac dysfunction Effective ventricular beats cannot be stimulated by the pacemaker while the ventricle is fibrillating Avoidance of excessive delay depends on immediate recognition of circulatory arrest and immediate institution of a prearranged program of resuscitation A cardiac monitor that presents an audible signal of each electric ventricular complex and sounds an alarm when the arrest occurs is available

Once cardiac arrest is recognized treatment must be instituted immediately without awaiting confirmation or diagnosis by electrocardiogram The heart may be mechanically stimulated by slapping the precordium cardiac puncture or massaging through the diaphragm while the electric pacemaker is being applied to the chest wall Ideally the pacemaker should be applied prophylactically before surgery to shorten the time delay between onset of arrest and stimulation to a few seconds If the pacemaker fails to resuscitate the patient within one minute the chest must be promptly

(9) N w E gl d J M d. 254 541 546 M r 2 1956

opened and the heart massaged In the presence of persistent ventricular fibrillation defibrillation should be attempted with electric shock of 60 cycle alternating current 150 volts for 0 15 second across large electrodes on each side of the heart

During these resuscitative procedures artificial respirations with oxygen is always necessary and intravenous transfusions of blood or other fluids and vasopressor drugs may be needed The patient must be constantly observed for two or three days because arrest recurs frequently and would be fatal without repeated stimulation The electric pacemaker should be attached and ready for instant use

Termination of Ventricular Fibrillation in Man by Externally Applied Electric Countershock is reported by Paul M Zoll Arthur J Linenthal William Gibson Milton H Paul and Leona R Norman[9] (Harvard Med School) in 11 episodes of ventricular fibrillation occurring in four patients during acute myocardial infarction after procaine amide intravenou ly for rapid arrhythmia in digitoxin intoxication or in Stokes Adams di ea e Fibrillation was successfully terminated each time The patient with Stokes Adams disease who was defibrillated on three eparate occasions recovered completely

Ventricular fibrillation usually rapidly fatal may occur in cardiac patients in any patient under anesthe ia in drowning and in electrocution It rarely stops spontaneously and treatment is unsatisfactory When it occurs in the operating room the patient may be resuscitated by opening the chest and restoring the circulation by manual systole The fibrillation may then terminate spontaneously after administration of drugs or after direct application of electric current countershock The latter usually consists of 60 cycle alternating current of 1 5 amp or more (120 150 volts) for 0 1 0 5 second applied across large electrodes on the heart

An external defibrillator that can effectively terminate ventricular fibrillation by application of the electrodes across the closed chest has been devised It consists of a special isolation step up transformer with a range of 0 720 volts The duration of the current is fixed at 0 15 second by a suitable condenser in a relay circuit The transformer and power re

( ) N w E gl d J Med 254 7 773 Ap 19 1956

lay contacts are capable of delivering 15 amp Copper electrodes 7.5 cm in diameter mounted on heavily insulated handles are smeared with electrode paste and held firmly in place against the chest wall at the level of the apex one to the left of the sternum and the other at the anterior axillary line Personnel should not touch the electrodes or the body of the patient nor should one person hold both electrodes

In the laboratory animal atrial fibrillation atrioventricular nodal tachycardia and ventricular tachycardia have been successfully terminated The procedure may prove clinically effective in stopping arrhythmias other than ventricular fibrillation

Defibrillation may be followed by ventricular standstill or recurrent fibrillation especially when associated with anoxia from prolonged circulatory arrest It may then be necessary to apply an external cardiac pacemaker to use the defibrillator repeatedly and to employ other resuscitative measures such as vasopressor agents and artificial respiration with oxygen

• [The development of methods of treating cardiac standstill and ventricular fibrillation by use of electrodes applied to the chest constitutes an important advance It is likely that these will be used routinely in the operating room in the case of surgical procedures on patients with conduction defects in the ECG or perhaps on all elderly subjects —Ed]

Experimental Prevention of Sudden Death from Acute Coronary Artery Occlusion in the Dog Elmer Milch Walter T Zimdahl Richard W Egan Ting Wei Hsin Arthur A Anderson and Joseph David[1] (Buffalo) describe the effects of quinidine thoracic sympathectomies and stellate ganglion blocks on standardized acute anterior myocardial infarctions induced by ligating the anterior descending coronary artery

Of 26 control dogs 11 died of ventricular fibrillation within ½ hour of ligation and 5 died within 24 hours (considered sudden death) The 10 survivors were killed two weeks later Typical anterior wall myocardial infarctions were found in all None of the dogs died of ventricular stand till in the first 30 minutes

Quinidine hydrochloride was given intravenously at the time of coronary artery ligation to another 26 dogs the rate of flow being governed by the response The total dose was 15 mg/kg body weight diluted with normal saline 18 ml/kg and administered over 45 minutes Eight of the dogs

(1) Am H J 50 485-491 Oct 1955

died of ventricular fibrillation within 30 minutes and four died during the following 24 hours

Staged bilateral thoracic sympathetic ganglionectomies were performed on 28 dogs and then the anterior descending coronary artery was suddenly occluded Within 30 minutes four dogs died of acute coronary occlusion and seven died during the ensuing 24 hours

In 50 dogs procaine was injected into the left stellate ganglion immediately after ligation of the descending coronary artery Six dogs died within 30 minutes of ligation and two others within 24 hours Ectopic ventricular beats were less numerous than in the other procedures

Thoracic sympathectomy and procaine injection of the left stellate ganglion protects the dog from ventricular fibrillation and death following coronary occlusion but quinidine is not significantly effective

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ELECTROCARDIOGRAPHY

Studies on Mechanism of Ventricular Activity XVI Activation of Human Ventricle Rashid A Massumi Alfred Goldman Louis Rakita Kiyoshi Kuramoto and Myron Prinzmetal made ECG studies of the ventricular wall by inserting straight 2 in long pieces of 0 020 gauge tempered silver wire to various depths intramurally Of 12 patients 7 had no heart disease 3 had mitral stenosis 1 constrictive pericarditis and 1 congenital heart disease The procedure was performed during thoracotomy required for the basic disease The left ventricle was studied in 11 patients the right in 1 Usually the free lateral wall midway between apex and base was explored The cavity of the ventricle was entered transmurally and ECG s were taken at various levels of the myocardium as the needle wire was withdrawn The procedure was completely devoid of hazard

Tracings from the subendocardium showed pure QS waves The positive component of the depolarization complex is generated almost entirely in the outer myocardial layers The subendocardium does not develop positive depolarization potentials For this reason lesions purely of the

( ) Am J Med 19 83 848 Dec 1955

subendocardium do not alter the QRS complexes Pathology in the epicardial myocardium such as inflammatory pericardial effusion and constrictive pericarditis lower the amplitude of the R wave Endocardial fibroelastosis encroaching on the subendocardial myocardium and producing a situation comparable to constrictive pericarditis but in a different location causes little change in QRS

The speed of impulse transmission through the human myocardial wall is not constant it is fast in the inner layer and 450 1 000 mm /second in the outer layers The subendocardium is also sluggish in generating injury potentials The same injury which produces S T segment elevation in the outer layers fails to produce significant displacement of the S T segments in the deeper layers Even profound injury to the subendocardial myocardium from a variety of causes produces no significant injury potential and no S T segment displacement Injury to the outer myocardial layers on the other hand produces marked S T segment elevation as seen in through and through myocardial infarction and acute pericarditis

The S T and T changes commonly found in subendocardial injury may be due to functional alterations in the outer myocardial layers of unknown but probably biochemical etiology These must be distinguished from the depression which is reciprocal to elevations on the opposite wall

In these experiments T waves were positive in the cavity and intramural leads T waves on the surface of the myocardium were usually positive but occasionally flat to inverted No gradient of potentials was found between the cavity intramural layers and epicardial surface in the repolarization potentials

Acute subendocardial infarction can be diagnosed when clinical symptoms are present with evidence of tissue necrosis with or without congestive heart failure but with normal QRS complexes Transient Q waves may disappear in two or three days An old subendocardial infarction has no characteristic ECG representation but the diagnosis should be considered in any patient with progressive congestive heart failure without obvious cause and with normal QRS complexes particularly if the history suggests coronary pain and myocardial infarction

• [The work of Prinzmetal and his colleagues is revolutionary in its implications It furnishes for the first time a rational explanation for many clinical observations These include the complete lack of parallelism between the degree of ECG change and the severity of an infarct as judged by clinical criteria Likewise the observation of Prinzmetal and his co workers indicates that comparatively minor stimuli such as alter ations in temperature or pressure or insignificant metabolic changes may lead to alterations in the T waves which are likely to be confused with those due to coronary artery disease This work emphasi es the necessity for basing the diagnosi of coronary disease—and for that matter other types of heart disease—primarily on clinical rather than on ECG evidence —Ed]

Unusual RT Segment Deviations in Electrocardiograms of Normal Persons were reported by L Guy Chelton and Howard B Burchell[3] (Mayo Clinic and Found) in a study of 100 patients with elevations of 1 mm or more in standard or precordial leads

In most patients the elevated RT segment presented as a U shaped or saddle shaped connection of the R and T waves in some instances 3 mm or more in height It was usually most elevated in the fourth and fifth precordial positions

In all patients the mean spatial vector of the sustained systolic potential was directed inferiorly anteriorly and to the left In general those with semivertical or vertical ECG positions had RT vectors directed anteriorly whereas those with horizontal or semihorizontal positions were directed toward the left axilla The vector could be demonstrated in the vectorcardiogram and the QRS loop was not completed to the isoelectric point

A primary diagnosis of functional illness was made in 46 patients Organic disease not related to heart disease was present in 23 and 10 had no symptoms and were considered in good health Of the 100 patients 32 had specific com plaints of chest wall pain

Although 18 patients had heart disease the ECG pattern was probably unrelated Mild angina pectoris was present in nine valvular lesions in eight and one patient had a history suggesting heart failure Three patients had coronary dis ease and the RT segments were depressed below the base line after exercise

The ECG pattern is normal although unusual but must be differentiated from the pattern of acute pericarditis or myo cardial injury The RT segment elevation was explained as

(3) Am J M S 30 54 60 J ly 1955

early repolarization in the subepicardial myocardium before activation or depolarization of the whole ventricle had been completed

QS and QR Pattern in Leads V_3 and V_4 in Absence of Myocardial Infarction Electrocardiographic and Vectorcardiographic Study was made by Borys Surawicz Robert G Van Horne John K Urbach and Samuel Bellet[4] (Gen l Hosp Philadelphia) in six groups of patients Twenty four had myocardial infarction 4 possible infarction 25 were without infarction in 4 infarction was considered unlikely 10 had left ventricular hypertrophy and 10 had no evidence of cardiovascular disease

A QS pattern or a significant Q wave in lead V_3 was found in 25 patients in whom myocardial infarction was considered absent (5 proved by autopsy) and in 6 patients in whom infarction was considered unlikely Most had left ventricular hypertrophy Only three patients had similar QRS patterns in V_4

The most significant differences between the groups with infarction and without infarction were in the low chest leads V_3 and V_4 recorded at the ensiform and epigastric level When lead V_3 was registered at the level of the ensiform (V_{3E}) an initial R wave was present in 24 of the 25 patients without infarction and in only 3 of the 24 with infarction Thus the initial deflection of the QRS at V_{3E} differentiated 84% of patients with from those without infarction The standard lead V_3 showed the same pattern in both group

In chest leads taken from sites above the standard level the QRS pattern was not significantly different in the group with and the group without infarction An initial R wave was more common in the high leads in patients with infarction

Vectorcardiography was not significant in differentiating the infarction from the noninfarction groups The greatest difference was in the initial 0 02 second of the QRS loop directed inferiorly in 90 92% of patients without infarction and in only 36 46% of those with infarction

Of patients with infarction who had a Q wave in the low chest leads at the ensiform or epigastric levels an initial R wave was present in lead aV_F in 50%

(4) C e l t m 12 391 40 S ptembe 1955

The inferior direction of the initial QRS vector and the low location of the point of origin of this vector rather than the low position of the whole heart seemed responsible for the absent initial R wave in leads V_3 and V_4 in patients without infarction

• [This article and the preceding one emphasize further the unreliability of uncritical use of the ECG in the diagnosis of recent or old myocardial infarction In the absence of a clear clinical picture such ECG changes as those described should be considered as being within the normal range—Ed]

Calcification of Pericardium in Apparently Healthy People Electrocardiographic Abnormalities Found in Tracings from Apparently Healthy Persons with Calcification of Pericardium are described by F A L Mathewson[5] (Univ of Manitoba) Of five patients studied calcification was diagnosed by x ray in four and at autopsy in one (accidental death) In three patients the RS T segments in lead II and the left precordium were definitely depressed Flat or inverted T waves occurred in the limb leads and the precordial leads in four patients The RS T segment depression and T wave inversion occurred in the opposite direction to the main QRS deflection None of the patients had notching of the P waves or auricular fibrillation This change may be uncommon in asymptomatic pericardial calcification

The ventricular complex abnormalities of pericarditis are characteristically restricted to the RS T segments and T waves the phase of repolarization During the acute phase the RS T segments are elevated and the T wave flat or inverted in one or more leads The changes tend to disappear with resolution of the process In chronic pericarditis the T waves are also flat or inverted but the RS T segment may be depressed These changes probably result from a disturbance of the subepicardial layer of the myocardium A residual adherent pericarditis may delay initiation of repolarization and proceeds in the reverse direction from the endocardium to the epicardium The voltages may be normal or abnormally high or low

Lack of calcification by x ray does not rule out pericardial scarring and normal ECGs may be found in the presence of recognizable pericardial calcification

5 Circulation 12 44 51 July 1955

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(4) Circulation 12 391 405 September 1955

Marvin Silverblatt[7] (Montefiore Hosp Pittsburgh) reviewed the records of 62 patients with pulmonary embolism of whom 29 recovered Autopsy was done on the other 33

Pulmonary embolism may be massive and fatal without inducing pulmonary infarction If the embolus is smaller it may cause infarction The massive emboli usually block the larger branches and the main stem of the pulmonary artery Cylindric clots usually arise in the femoral and external iliac veins whereas thicker masses with treelike branches come from the internal iliac bed usually the uterine veins In massive emboli death is so sudden that there is inadequate time for infarction and secondary changes Usually the lungs are only slightly edematous and hyperemic and the right ventricle dilated

Autopsy showed infarction in 24 of the 33 patients usually pyramidal or wedge shaped with the base directed pleurally and the apex at the site of vascular occlusion Fresh infarcts were not sharply defined Passive congestion was present in 37 of the 62 patients

An obstruction interposed between the two ventricles can produce three types of symptoms—insufficient flow from the left ventricle with peripheral circulatory failure and shock signs of pulmonary infarction and signs of right ventricular failure

The shock syndrome of tachycardia hypotension pallor cool clammy skin and diaphoresis occurred in 50% of the patients Signs of pulmonary infarction occurring in 58% included severe dyspnea and chest pain in 30 patients cough and hemoptysis in only 10 and rales rhonchi pleural friction rub consolidation and pleural effusion in 37 X ray evidence was present in 19 No specific x ray configuration was noted the wedge shaped shadow being neither classic typical nor common

Due to sudden obstruction to flow from the right side of the heart the right ventricle dilates and rotates Right heart failure supervenes Cervical vein distention and enlargement of the liver occur but peripheral edema is rare because patients are usually bedfast

In 37 patients apprehension and related mental symptoms preceded evidence of a major pulmonary embolus Restless

(7) A M A Arch Int Med. 96 19 2 July 1955

The wide use of routine ECG s will include persons with asymptomatic pericardial scarring Chronic pericardial scarring may explain the tracing with normal QRS complexes and T wave abnormalities particularly if the T waves are opposite in direction to the main QRS deflection and associated with depressed RS T segments Low QRS voltage may or may not be present Diagnosis is even more likely if serial tracings reveal that the abnormalities remain constant for years

Electrocardiographic Diagnosis of Acute Myocardial Ischemia Gordon B Myers and Frederick N Talmers[6] (Wayne Univ) distinguished the pseudodepression of the S T segments *seen with tachycardia from the abnormal de*pression secondary to acute subendocardial injury by correlation with autopsy findings In pseudodepressions the S T segments display a continuous ascent in an arc of upward concavity In depressions due to myocardial abnormality they have characteristic horizontal or sagging depressions of 1 mm or more Cardiac glycosides must be excluded as the cause of the depression

The two step exercise tolerance test was used for establishing the diagnosis of coronary insufficiency when no clear cut evidence was obtainable The test was useful for prognosis in asymptomatic ambulatory patients after recovery from myocardial infarction In these tests it is important to recognize pseudodepression a drop of the S T junction 0 5 mm or more while the S T segment continuously ascends in a concave curve A positive response to the exercise test is also manifested by depression of the S T junction by 0 5 mm or more but the S T segment is horizontal or sagged Abnormal S T displacements were more frequent in leads V_4 and V_6 which face the anterior or anterolateral aspects of the apex

The ECG abnormalities localized to right precordial leads may be associated with septal ischemia and those localized to the back *leads or to* aV_F *with posterior ischemia* The chest leads are more frequently positive than are the standard leads

Pulmonary Embolism Review with Emphasis on Clinical and Electrocardiographic Diagnosis Seymoure Krause and

(6) A n I t Med 43 561 582 Augu t 1955

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Pulmonary embolism may be massive and fatal without inducing pulmonary infarction If the embolus is smaller it may cause infarction The massive emboli usually block the larger branches and the main stem of the pulmonary artery Cylindric clots usually arise in the femoral and external iliac veins whereas thicker masses with treelike branches come from the internal iliac bed usually the uterine veins In massive emboli death is so sudden that there is inadequate time for infarction and secondary changes Usually the lungs are only slightly edematous and hyperemic and the right ventricle dilated

Autopsy showed infarction in 24 of the 33 patients usually pyramidal or wedge shaped with the base directed pleurally and the apex at the site of vascular occlusion Fresh infarcts were not sharply defined Passive congestion was present in 37 of the 62 patients

An obstruction interposed between the two ventricles can produce three types of symptoms—insufficient flow from the left ventricle with peripheral circulatory failure and shock signs of pulmonary infarction and signs of right ventricular failure

The shock syndrome of tachycardia hypotension pallor cool clammy skin and diaphoresis occurred in 50% of the patients Signs of pulmonary infarction occurring in 58% included severe dyspnea and chest pain in 30 patients cough and hemoptysis in only 10 and rales rhonchi pleural friction rub consolidation and pleural effusion in 37 X ray evidence was present in 19 No specific x ray configuration was noted the wedge shaped shadow being neither classic typical nor common

Due to sudden obstruction to flow from the right side of the heart the right ventricle dilates and rotates Right heart failure supervenes Cervical vein distention and enlargement of the liver occur but peripheral edema is rare because patients are usually bedfast

In 37 patients apprehension and related mental symptoms preceded evidence of a major pulmonary embolus Restless

(7) A M A Arch Int Med 96 19 25 July 1955

ness apprehension irritability discomfort nervousness twitching and other *manifestations* were often present

The pattern of acute cor pulmonale in the ECG includes (1) development of an S wave in lead I (2) depression of the S T segments in leads I and II with *staircase* ascent of the S T segment *in other leads* (3) flattened to inverted T waves in limb leads II and III (4) a Q wave in limb leads III and aV_F (5) tall peaked *P* waves in leads II and III (6) *various degrees of intraventricular block of the right* bundle branch system and even development of right heart strain with inversion of T waves *in one or more precordial* leads (7) clockwise *rotation* of the heart with movement of the transition zone to the left in the precordial leads, (8) development of a *vertical position* and (9) evidence of superimposed coronary insufficiency Frequent serial tracings begun early are necessary to demonstrate slight and transient changes

Electrocardiogram in Electrolyte Imbalance According to Samuel Bellet[8] (Univ of Pennsylvania) the ECG can detect electrolyte imbalance particularly deviations in calcium and potassium levels Changes have been produced by alterations in serum magnesium but sodium level has *no* effect except that acid base imbalance may alter the potassium influence Electrocardiograms *reflect local electrolyte* changes in the heart *not necessarily* associated with significant deviations in serum electrolytes

In pure hypocalcemia the prolonged *Q T* segment involves only that portion between the QRS and the T wave The isoelectric line between these deflections is lengthened occasionally to twice normal and the T wave may be inverted The lengthened Q T segment may be accompanied by a lengthened mechanical systole *In hypopotassemia only* the electrical systole is prolonged while mechanical systole is unaffected Calcium administration does not alter the prolongation due to hypopotassemia nor does potassium alter the Q T interval of hypocalcemia Increased serum calcium shortens the Q T interval below normal and in diseased hearts may cause extrasystole paroxysmal tachycardia and even death

(8) A M A A h I t M J 96 618 639 N ember 1955

In hypopotassemia the P wave may be increased in amplitude during tachycardia because the preceding U wave is superimposed on the P wave The QRS complexes are also increased the S T portion of the Q T segment prolonged the U wave increased in amplitude and often superimposed on the terminal portion of the T wave the ST segment depressed the T wave inverted and arrhythmias particularly supraventricular tend to appear No single pattern is pathognomonic of hypopotassemia and the changes occur in various combinations Similar changes have been induced by other diseases In 15 biopsies of deltoid muscle the ECG changes in hypopotassemia were better correlated with the serum potassium than with intracellular potassium

The effects of hyperpotassemia may be divided into four stages increased amplitude of the T wave with narrowing of the base sinus pauses and irregular heart rate widening of ventricular complexes and lastly a slow idioventricular rhythm with increasing width of ventricular complexes In mild hyperpotassemia the patterns are not characteristic and the diagnosis is difficult until the serum potassium reaches 7 0 mEq /L and over

Hypertension and azotemia are frequently associated with hyperpotassemia and the initial tracing may present a pattern of left ventricular hypertrophy With hyperpotassemia the inverted T waves in lead I and the left precordium frequently become more inverted and peaked while the upright T waves in the right precordium (leads V_1 V_3) become higher and peaked In myocardial damage of various types with inversion of T waves from V_1 to V_6 hyperpotassemia causes the T waves to become less inverted flattened and finally upright In the presence of transmural infarction the inverted T waves often become more inverted and peaked

The effects of hyperpotassemia may be obscured by pre existing T wave inversion left ventricular hypertrophy patterns bundle branch block myocardial infarction alterations in other electrolytes and digitalis

The characteristic ECG findings of hypopotassemia may by obscured by pre existing heart disease marked left ventricular hypertrophy bundle branch block anoxia digitalis and other electrolyte changes particularly calcium possibly

magnesium and, indirectly sodium and phosphate concentration

Concealed Conduction Further Evaluation of a Fundamental Aspect of Propagation of Cardiac Impulse is presented by Richard Langendorf and Alfred Pick[1] (Michael Reese Hosp) Concealed conduction consists of incomplete penetration of pre formed conduction pathways by an apparently blocked impulse and is manifest by its effect on conduction or formation of a subsequent forward or retrograde impulse

The commonest example of concealed A V conduction affecting transmission of a subsequent impulse is the compensatory pause after ventricular premature systoles and the P R prolongation after the ventricular premature beat Concealed conduction is responsible for double or multiple blocking of consecutive auricular impulses at slow normal or moderately rapid rates Above rates of 200 failure of the A V junction to respond to consecutive impulses can be explained by physiologic interference and abnormal block

The effect of concealed conduction on formation of impulses is manifest by altering the expected appearance time of impulses of a subsidiary pacemaker In A V dissociation the regular cycle of a nodal pacemaker may be periodically disturbed by partially transmitted sinus impulses In second degree A V block nodal escapes may fail to occur when expected The phase of concealed A V conduction i e, the period between absolute and relative refractory phases during which impulses penetrate into the A V junction without traversing it can sometimes be sharply delineated in terms of R P intervals

These principles can account for certain phenomena associated with impaired intraventricular conduction Thus concealed intraventricular conduction may account for the rarity of second degree bundle branch block continuation of aberrant ventricular conduction in supraventricular tachycardia the pattern of impulse spread in certain cases of ventricular pre excitation and variations in appearance and coupling of ventricular premature systoles

When two consecutive auricular impulses fail to traverse

(1) Circulation 13 381 399 March 1956

the A V junction the mechanism of concealed A V conduction should be considered Concealed conduction may cause delayed transmission partial penetration (repetitive concealed conduction) or complete blockage of the subsequent impulse Repetitive concealed conduction responsible for repetitive concealed discharge of the subsidiary pacemaker may account for prolonged ventricular asystole

Recognition of concealed conduction is indispensable for understanding disturbances of conduction and formation of the cardiac impulse

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PATHOLOGIC PHYSIOLOGY

Relation of Age to Certain Measures of Performance of Heart and Circulation Milton Landowne Martin Brandfonbrener and Nathan W Shock analyzed the resting cardiac output in relation to intra arterial pressure in 67 persons to estimate the peripheral circulation and cardiac performance

Systolic pressure gradually increased from an average of 115 mm Hg in the third decade to 144 mm Hg in the ninth Diastolic pressures remained fairly constant and the true mean pressures changed only insignificantly Mean heart rate declined with age The ratio of pressure to flow a measure of total vascular resistance of the greater circulation increased with age Reduction in tissue perfusion or increased resistance was significant and greater than reductions in oxygen uptake carbon dioxide production or intra cellular water indicating reduced cellular perfusion

These observations reflect a decrease in useful cardiac work as the calculated pressure component increase was not comparable with the decrease in output The estimated duration of systole does not shorten but increases The result is a decrease in calculated work performance or power The increase in pressure component of work decrease in power and increase in relative heart size indicate reduced effective reserve of the left heart as a muscle pump

Cardiac reserve tends to diminish with age even in subjects without evident clinical cardiac abnormality

• [The importance of senescence of the myocardium has been emphasi ed

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by William Dock who has applied the term presbycardia to heart failure occurring in elderly patients without evidence of hypertension valvular disease myocarditis or significant degrees of coronary narrowing The concept is an important one because it explains why loads whether due to valvular disease hypertension thyrotoxicosis or other causes which are readily tolerated by young persons tend to produce cardiac failure in elderly subjects In most instances the aging process alone does not lead to clinically significant cardiac manifestations However when the process is sufficiently advanced congestive failure may occur in the absence of any pathologic findings other than dilatation and hypertrophy The work of Landowne *et al* is significant in that it furnishes a firm physiologic basis for Dock s concept of presbycardia or what may also be called the senile heart —Ed]

Respiratory Insufficiency and Chronic Cor Pulmonale According to Irving Mack and Gordon L Snider[3] (Michael Reese Hosp) work capacity is limited by the cardiocirculatory system not the respiratory system Dyspnea is a common symptom of respiratory insufficiency Primary cardiac disease with secondary pulmonary congestion must be excluded as its cause Wheezing chronic cough and recurrent lower respiratory infection suggest respiratory insufficiency as the cause of dyspnea The chest is frequently fixed near inspiration diaphragmatic and chest excursions are decreased and the upper abdominal wall may paradoxically bulge during expiration Prolonged expiration can be detected at the bed side Rhonchi or localized wheeze are diagnostic and must be sought during quiet and forced expiration Frequently a wheeze can be heard only over the dependent lung with the patient in the lateral recumbent position Increased anteroposterior diameter decreased breath sounds and rales are not specific Chest x rays in full inspiration and expiration are helpful but fluoroscopy gives the most information Pulmonary function studies complete the evaluation

Chronic cor pulmonale is right ventricular hypertrophy due to bilateral and diffuse pulmonary disease or pulmonary circulatory disease Chronic diffuse obstructive emphysema due to chronic bronchitis is the most common cause of chronic cor pulmonale in the United States Bronchial asthma is responsible only if severe and of long duration with secondary infectious bronchitis Kyphoscoliosis tuberculosis and sarcoidosis may cause chronic cor pulmonale Involved pulmonary vessels repeated pulmonary emboli primary pulmo

(3) Circulation 13 419 447 March 1956

nary hypertension sickle cell anemia with multiple capillary thromboses schistosomiasis with obliterating endarteritis granulomatous or fibrous interstitial proliferation and perivascular lymphatic carcinomatosis may also cause chronic cor pulmonale

Diagnosis of early chronic cor pulmonale depends on suggestive findings It should be suspected in chronic obstructive emphysema and is indicated by arterial blood abnormalities secondary polycythemia or right ventricular hypertrophy Digital clubbing and hypertrophic osteoarthropathy may occur with small focal pulmonary lesions and are not pathognomonic Accentuation of the pulmonic second sound is an early sign The earliest x ray abnormality is an enlarged pulmonary artery trunk Hypertrophy of the right ventricle is undetectable by x ray and becomes visible only after dilatation Electrocardiographic abnormalities occur late and reveal a more vertical heart rotated clockwise The QRS complexes may be of low voltage and P pulmonale may be present An rsR complex in the right precordial leads is evidence of right ventricular strain and a typical right ventricular hypertrophy pattern (relatively tall late R in aV_R V_{4R} or V_1) is evidence of chronic cor pulmonale Right heart catheterization the best method for early detection is not yet justified as a routine procedure

The best treatment of chronic cor pulmonale is prevention Recurrent or lingering bronchitis should be vigorously treated and if chronic obstructive emphysema is present acute respiratory infection should be treated as major illnesses Impending circulatory and pulmonary breakdown may be predicted by increasing pulmonary insufficiency polycythemia and blood gas abnormalities

Congestive heart failure can be alleviated only if the pathologic pulmonary changes are at least partially reversed Infection must be treated an adequate airway provided and alveolar ventilation improved by antibiotics bronchodilator drugs sputum liquefiers breathing exercises and occasional bronchial aspiration Adrenal corticosteroids must be used with caution Pneumoperitoneum and abdominal belts are disappointing Treatment of hypoxia is essential Oxygen should be well humidified in low concentration intermittent and given only when the patient is under constant observa

tion by a physician not a nurse A mechanical respiratory aid may be used with oxygen to hyperventilate the patient Respiratory depressant drugs such as morphine are strongly contraindicated

Specific cardiac therapy may be effective if combined with pulmonary measures Digitalis definitely improves cardiac function in chronic cor pulmonale with congestive failure and should be continued indefinitely after failure has been corrected Mercurial diuretics salt restriction and rest are important When the hematocrit value is above 55 removal of 300 500 ml blood every three to five days to bring the value to 50 and the hemoglobin value to 14 Gm is advisable

Low Sodium Syndromes E Gordon Margolin and John P Merrill[4] (Peter Bent Brigham Ho p Boston) present suggestions for diagnosis and treatment of hyponatremia Low sodium concentration in the serum may be caused by several factors such as dilution by retention of water more than retention of sodium depletion of body sodium or redistribution of sodium or water in the body

History physical examination and a few laboratory tests may distinguish these factors Helpful criteria are knowledge of normal weight and recent weight changes presence or absence of edema and dehydration recent intake and output of fluid consumption of food vomiting diarrhea and perspiration and cardiac failure hepatic insufficiency renal impairment or terminal cancer

Serum protein hemoglobin or hematocrit carbon dioxide chloride potassium nonprotein nitrogen and urinary sodium values should be obtained The sodium content of other body secretions if available may be helpful

In hyponatremia due to dilution the total body water is markedly increased and the patient has a form of water intoxication Both the extra and intracellular spaces are diluted and no evidence of sodium loss is found Associated findings include nitrogen retention low hematocrit serum protein and urinary sodium values Severity of symptoms usually depends on rapidity with which the abnormal state develops

The ideal treatment is restriction of water intake A pa

(4) GP 11 59 69 May 1955

tient given no water will lose 500 800 cc water daily through the skin and lungs and even more in the presence of fever and increased respirations General supportive measures may help Hypertonic saline infusions only expand the extracellular water further and may possibly precipitate serious congestive heart failure

In hyponatremia due to sodium depletion body sodium is truly deficient and body water low or normal Usually this results directly from stringent therapy such as rigid dietary salt restriction especially when resins are added postoperative glucose and water solutions in large amounts without saline frequent mercurial diuresis repeated mechanical removal of large volumes of salt containing fluids replaced by water only as in paracentesis thoracentesis Southey tube drainage and intestinal and gastric drainage severe vomiting diarrhea or profuse perspiration and renal salt wasting due to impaired renal function or deficient adrenocortical hormones

The patient is dehydrated and acidotic serum sodium and chloride levels are low and the nitrogen level is high He is weak and drowsy and has muscular cramps thir t unrelieved by water anorexia nausea and vomiting Urinary output is low and he is refractory to diuretics Tongue and skin are dry the skin is inelastic and cool temperature may be low peripheral veins are collapsed and orthostatic hypotension may be present If the syndrome is not corrected he becomes restle s confused and hypotensive and shock and coma develop

Dramatic success often follows salt replenishment orally when possible Hypertonic solution 3 or 5% intravenou ly hould be limited to 200 cc of the 5% solution over four hours and no more than 400 cc daily Venous pressure elevation or pulmonary edema forbodes serious complications After a third of the calculated deficit is replaced the condition should be re evaluated If there is either no improvement or deterioration clinically or chemically therapy shoud be discontinued before excessive amounts of saline are given If improvement has occurred more salt can be given

For example a 70 kg man has a serum sodium concentration of 120 mEq /L Total body water (53% of body weight) is 37 kg The total sodium deficit is 142 — 120 or 22 mEq /

L 22 mEq/L × 37 L = 814 mEq Since each gram of NaCl equals 17 mEq he will require 814 mEq − 17 or 48 Gm NaCl *In a 5% solution this is about 900 cc He should* receive only 300 cc the first day and the condition should then be re evaluated

Hyponatremia due to redistribution results from metabolic abnormalities in which sodium enters the cell and potassium is extruded The total body sodium may be normal but the serum sodium concentration low This can be rectified only by correcting the underlying disease and not by adding excess sodium It is seen in postoperative patients chronic stress long standing wasting illnesses cachexia chronic congestive heart failure terminal carcinoma and severe tuberculosis There may be no symptoms of electrolyte disturbance despite the fact that serum and urine sodium levels are dropping The hyponatremia is the only manifestation of the disease

Measurement of serum sodium concentration is not enough Careful evaluation of history physical findings and laboratory data is required Treatment of the chemical derangement may sometimes produce dramatic clinical improvement but it is not always indicated and may aggravate the clinical situation Judicious clinical appraisal and cautious therapeutic maneuvers are important

Essential Pulmonary Hypertension Report of Clinical Physiologic Studies in Three Patients with Death Following Catheterization of Heart is presented by H Schafer J M Blain K Ceballos and R J Bing (Med College of Alabama) In this condition increased pulmonary artery pressure results from increased vascular resistance in the lung The exact cause of these vascular changes is unknown but in some patients may be due to repeated asymptomatic pulmonary emboli Two patients were under age 15 and the third was 33 All three died after cardiac catheterization was completed

Both children had effort syncope in one accompanied by palpitations cyanosis and precordial pain All three had history of shortness of breath particularly severe in the adult and present at rest in two A *systolic murmur* was heard in all three and a diastolic murmur in two These murmurs sometimes cause diagnostic errors as they may occur in con

(5) A Int M d 44 505 3 2 M h 1956

genital and rheumatic heart disease All patients with essential pulmonary hypertension have an accentuated second pulmonic sound The ECG s showed right axis deviation and right ventricular hypertrophy and fluoroscopy revealed increased hilar and diminished peripheral pulmonary vascular markings with prominent right ventricle and pulmonary artery segment The most significant finding by cardiac catheterization was pronounced increase in pulmonary artery pressure As the physical condition contraindicated collection of expired air and arterial blood samples cardiac output and pulmonary vascular resistance could not be calculated

After catheterization sinus tachycardia developed in one patient followed by 2 1 or 3 1 A V block and a ventricular rate of 125/minute that slowed to 50/minute and then ventricular standstill with an auricular rate of 50 In the second patient ventricular rate suddenly slowed from 140 to 30 beats/minute with complete cessation of auricular complexes In the third patient ventricular tachycardia developed Autopsy performed in two patients revealed medial and intimal thickening of the pulmonary arterioles leading to almost complete occlusion of the lumens and arteriosclerotic changes in the pulmonary artery

Death in the three patients may have been due to reflex vagal stimulation or acute failure of the right ventricle Inability to increase cardiac output leads to relative coronary insufficiency and cerebral i chemia The latter are due to limitation of cardiac output so that increased oxygen cannot be upplied to the heart mu cle and decline in peripheral blood flow ensues

Patients with e sential pulmonary hypertension are in continual danger of sudden death Usually harmless diagnostic procedures such as determining the circulation time with decholin ® barbiturate anesthesia or catheterization may be fatal Such procedures should be done with great care The present instances were the only fatalities in over 900 cardiac catheterizations during the preceding 3½ years

Distribution of Flow through Pulmonary Manifold simulating some dynamics of the pulmonary circulation was tudied by Simon Kodbard[6] (Michael Reese Ho p) Clinical

(6) Am H rt J 51 106-1 6 J y 1956

terminology was applied to mechanical apparatus in the experiment

APPARATUS—In the basic model a hanging reservoir simulating the right ventricle provided a constant pressure head A rotameter between this reservoir and the manifold gave a measure of total flow Fluid passed from the reservoir through a wide tube into a manifold which divided it into four smaller tubes (arterioles) 10 cm apart. Arrangements were varied to test specific effects Dynamics of flow through a rigid system was compared with effects of introduction of soft walled capillary tubes (Penrose tubing 3 cm long and 6 mm in diameter) Outlets of all four tubes were placed at the same level equal to that of inflow A separate outflow was available for each

Vertical positioning of the pulmonary manifold caused preferential flow through the dependent channels while little perfused the elevated portions This effect was exaggerated at low pressure heads As the pulmonary arterial pressure head was raised elevated or apical segments received an improved supply Slight to moderate intrapulmonary air pressure uniformly applied to all four capillaries shunted flow away from the elevated vessels and increased that through the dependent tubes High levels of such air pressure reduced flow as a whole and resulted in need of a high pulmonary arterial pressure if normal flow was to be perfused through the lung Elevation of level of the outlet (pulmonary venous pressure) increased flow through elevated segments until it equalled that through the base When the (intrapulmonary) air pressure was then raised apical flow was *markedly reduced and almost the entire flow shunted* through the dependent channels

Rise in pulmonary venous pressure may produce anomalous increases in total delivery superimposition of alveolar pressure can bring about striking variations in distribution of flow through a pulmonary system Enhancement of precapillary resistance equalized flow through the elevated and dependent portions of the manifold but reduced total flow for a given pressure head thereby requiring a higher arterial pressure to maintain perfusion of the system at normal flow rates Elevation of intrapulmonary air pressure in the e circumstances had only limited effect in redistributing flow to the base

Thus several independent factors—pressure head (pulmonary arterial pressure) altitude (position) of various

segments of the lung precapillary (arteriolar) resistance intra alveolar pressure and pressure level at outlet (pulmonary venous pressure)—may be important in delivery and distribution of pulmonary blood flow Changes in body position as in recumbency can redistribute the blood supply and increase flow to the pulmonary apical segments furnishing one explanation of apical localization of reinfection tuberculosis in the adult and for recumbent therapy The upright position may act to reduce blood flow to the apex accounting for differences in gas content in various lung segments in rate of lymph drainage and in distribution of blood from the two venae cavae Higher incidence of tuberculosis in patients with pulmonic stenosis accords with this interpretation

Emphysema and rapid progression of apical tuberculosis often go together Progressive rise in intrapulmonary air increases the impediment to flow through the lungs and demands relative pulmonary hypertension which provides increased flow to the apexes but this enhances the tendency to basilar *congestion transudation* and edema These *may* be countered by external positive pressure or by development of positive intrapulmonary pressure by spontaneous air entrapment which occurs in emphysematoid respiration The present experiments suggest that flow through the apex may thereby be further reduced If the alveolar air pressure were raised excessively the added load on the right heart might cause failure and lead to chronic cor pulmonale In pulmonary venous hypertension as in stenosis or mitral insufficiency or left heart failure flow through the apex may be enhanced It is perhaps significant that apical tuberculosis is statistically less frequent in patients with mitral stenosis

A raised outlet (pulmonary venous) pressure may produce significant increase in flow apparently due to increased distention (diameter) of the elevated vessels Increase in lateral pressure on all pulmonary capillaries may bring dependent capillaries closer to transudation and edema This may be counteracted by an increase in alveolar air pressure Heightened resistance at the outlet causes generalized pulmonary hypertension involving outflow tract capillaries and arterial branches engorged capillaries lead to danger of pulmonary edema By contrast pulmonary arterial hypertension as in

emphysema and some congenital anomalies may affect only the pulmonary arterial tree with no threat of pulmonary congestion or edema

Unequal air distributions and air entrapment may occur in emphysema in left heart failure and even in normal persons Slight air entrapment can virtually stop flow through an elevated segment while flow through a dependent segment is hardly affected suggesting that in pulmonary congestion the restlessness and frequent change of position may be a protective response Hypostatic pulmonary congestion and pneumonia of unconscious patients probably result from loss of this protective mechanism

Interposition of a precapillary resistance between the right heart and pulmonary capillaries can achieve relatively uniform distribution of flow through the lung thus improving ventilatory respiratory function Redistributive effects of intrapulmonary air pressure on flow distribution are reduced in presence of heightened precapillary resistance and flow through the elevated portions of the lung is not diminished as drastically as when the pulmonary arterioles provide little resistance to flow Benefits obtained in protection of the pulmonary capillary against transudation and in relatively uniform distribution of pulmonary blood flow are thus paid out of increased work load of the right ventricle The blood supply of the lung parenchyma probably does not share directly in distribution of the pulmonary arterial blood flow but probably affects it indirectly through anastomoses of bronchial with pulmonary arterioles Pulmonary arteriovenous fistulas can provide bypaths through which unoxygenated blood may enter the systemic circulation competing with normal pulmonary vessels for the right ventricular output If resistance to flow through the pulmonary vessels is increased by congenital heart disease enhanced intrapulmonary air pressure or arteriolar sclerotic change flow through the shunt may be enhanced

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MISCELLANEOUS

Hyperventilation Syndrome Frances Ames[7] (Cape Town Union of South Africa) reports 40 cases The syndrome is di

(7) J M t Sc 101 466 5 5 J 1 1953

tinctive and is due to increase in depth and rate of breathing which is nearly always the result of emotional stress Sighing dyspnea can be differentiated from dyspnea of organic disease by careful history taking Late inversion of T waves S T depressions and sinus tachycardia have all been reported due to hyperventilation and when combined with precordial pain have led to erroneous diagnosis of myocardial infarction

Of the 40 patients only 3 realized that they were over breathing though 24 admitted to respiratory difficulty when directly asked The characteristic and striking feature of the respiratory difficulty was that it was never related to exertion Hyperventilation commonly took the form of deep and fairly rapid breathing In only two patients was breathing very fast and shallow or panting

Some cerebral symptoms were present in 31 patients The most common was giddiness faintness or lightheadedness—never true vertigo always aggravated by upright posture and relieved by recumbency and often accompanied by blurring of vision or spots before the eyes Drowsiness with yawning was often seen after a hyperventilation test and loss of inhibition was common Several patients had a feeling of unreality or behaved abnormally Peripheral nerve involvement was manifested by paresthesias starting in the hands and feet and later becoming generalized in a few patient progressing to tetanic spasm The commonest gastrointestinal disturbance was distention of the stomach probably due to air swallowing during overbreathing

Circulatory di turbances comprised precordial pain palpitations and coldness of the extremities Fatigue was common In one patient the pain had all characteristics of angina but apparently was never provoked by any form of exercise but hyperventilation One patient had a burning feeling under the sternum after a few minutes of overbreathing another a sharp substernal pain radiating to the left shoulder and neck another a dull ache over the left precordium two sensation of oppression in the left precordium and two sharp stabbing pains in the left mammary region

Within a few seconds of overbreathing alveolar CO ten sion drops from normal of 40 to 15 20 mm Hg and despite continued overbreathing does not diminish much further Many clinical symptoms are due to resulting alkalemia Cer

ebral circulation is sensitive to chemical changes in the blood and diminishes as the CO_2 content falls In patients who overbreathed a CO_2-rich mixture the characteristic cerebral symptoms did not develop and once the symptoms appeared they were rapidly relieved by rebreathing CO_2

As a direct result of overbreathing reflex peripheral vasoconstriction occurs This is one of the factors producing peripheral neurologic symptoms though the prime factor is alkalosis Tetany is a manifestation of peripheral nerve involvement

Diagnosis is not difficult An accurate history of periodic attacks of peripheral and central nervous system disturbances and respiratory distress unrelated to exertion makes the diagnosis certain and a hyperventilation test clinches the diagnosis when the symptoms are reproduced Differential diagnosis includes neurosis or functional disease epilepsy hypoglycemia thyrotoxicosis peripheral vascular disease poliomyelitis organic cardiac disease Da Costa s syndrome tetany and acroparesthesia If careful attention is paid to all symptoms and not just to the chief complaint correct diagnosis can be made

Medication is usually not necessary except for sedation in anxious patients Calcium is of doubtful value Ammonium chloride has been reported effective in preventing alkalosis The hyperventilation test is not only diagnostic but therapeutic because fears of serious organic disease are immediately allayed when the symptoms are reproduced by overbreathing It is difficult to overventilate through the nose and the value of nasal breathing in preventing hyperventilation is emphasized Breath holding or rebreathing into a paper bag or hat brings relief The emotional stress which causes hyperventilation usually needs minor treatment Psychotherapy is not always necessary and patients usually adjust well if given an opportunity to discuss their problems

• [The hyperventilation syndrome is probably the commonest cause of recurrent weak spells A feeling of unreality and of faintness is common but actual loss of consciousness is exceptional if it ever occurs Amnesia is not unusual and many patients believe they have actually been unconscious during the episodes The precise mechanism of the chest pain occurring in some patients is uncertain but it is possibly related to increased tension in the thoracic muscles resulting from carbon dioxide deficiency The syndrome frequently occurs in patients who have other causes of spells and then may be an aggravating factor Thus there are

some individuals with spontaneous hypoglycemia who do not show all their symptoms when given insulin alone or when subjected to hyperventilation only but who exhibit the full blown pattern of the spontaneous episodes when hyperventilating during an insulin reaction Likewise there are patients with postural hypotension who only have the symptoms when they change position after having breathed excessively

In management of the hyperventilation syndrome three features are important The first is reproduction of the patient's symptoms by voluntary hyperventilation and preferably on repeated occasions The demonstration that the doctor and the patient himself can turn the symptoms on and off at will is likely to overcome much of the anxiety associated with the syndrome The second feature of management is emphatic reassurance with explanation concerning the physiologic mechanisms whereby hyperventilation leads to cerebral vasoconstriction increased muscle tension and often distention of the stomach The third feature of management is teaching the patient to block the mouth and nose for fifteen seconds then take a small breath and repeat the procedure until the symptoms are terminated In most instances these measures suffice to relieve the syndrome When they are ineffective more formal psychotherapy will usually be necessary—Ed.]

Syndrome of Hypersensitive Xiphoid was studied by Mack Lipkin Lyman A Fulton and Edward A Wolfson[8] (New York Hosp—Cornell Univ Med Center) Among 200 unselected patients 6 had tender xiphoids and 4 of the 6 had chest symptoms suggesting the syndrome The pain most commonly is a deep slightly nauseating ache rarely burning never a stabbing pain At night it often interferes with sleep When it occurs during exertion the activity may or may not be stopped in contrast with angina pectoris which usually compels stopping

Onset and disappearance of pain are not instantaneous Duration varies from minutes to hours with recurrences in minutes hours or days If untreated the syndrome may last for weeks more commonly for months and rarely for years usually disappearing spontaneously Precipitating causes are obscure and varied Bending stooping lifting turning over in bed eating a large meal and walking especially up an incline are common causes of renewed pain

Diagnosis is easy if suspected The xiphoid area should be palpated in all patients with pain in the chest or upper abdomen When the syndrome is present remarkably little pressure causes considerable pain and duplicates the symptoms The syndrome is often associated with coronary artery disease gallbladder disease peptic ulcer esophageal lesions and hiatus hernia

(8) N w E la d J Med 53 591 597 Oct 6 1955

Infiltrating the area with procaine the most effective therapy usually produces lasting relief Sometimes a second infiltration is necessary and occasionally a third Ethyl chloride spray may relieve an acute attack and the prompt occurrence of relief may aid in diagnosis When xiphoidalgia is associated with other disease control of the major disease may be followed by disappearance of xiphoidalgia The pain characteristically produces anxiety and the patient believes he has heart disease Even when procaine infiltration fails the pain will disappear spontaneously in weeks or months Xiphoidectomy is indicated only in patients with severe prolonged pain unresponsive to other therapy

The syndrome of hypersensitive xiphoid is probably commoner than generally appreciated It should be considered oftener in the differential diagnosis of pain in the chest or abdomen

Primary Tumors of the Heart Henry P Goldberg and Israel Steinberg[9] (New York Hosp—Cornell Med. Center) reviewed the classifications diagnosis and treatment of cardiac tumors Incidence of primary tumors was rare only 0 0017 % of 480 351 autopsies

Almost all intracavitary tumors originate in the atria Characteristically the syndrome mimics mitral or tricuspid valvular involvement without a history of rheumatic fever Exertional dyspnea is common and cardiac failure intractable Cardiac output is reduced angina may be present and systolic pressure is often low Fragmentation of the tumor may lead to emboli Other features are arrythmia syncope unexplained episodes of dyspnea cyanosis and orthopnea Symptoms and auscultatory signs may vary with change of position

In seven patients catheterization revealed obstructed outflow from the involved atria and elevated atrial pressure Definitive diagnosis depends on angiocardiography with characteristic filling defects in an enlarged atrium Mural thrombi do not produce filling defects and those due to a regurgitant stream from tricuspid insufficiency are transient An atrial obstructing thrombus (ball valve or pedunculated) has not been reported by angiocardiography but roentgen

(9) Ci lat o 11 963 9 0 Ju 195

findings would be similar to those of intracavitary tumor Surgery should be considered for both conditions

Myxoma commonest intracavitary tumor has been reported in patients aged 3 months to 68 years It usually arises by a small pedicle from the atrial septum in the region of the fossa ovalis About 75% are in the left atrium

The other intracavitary tumors were sarcomas of all histologic types predominantly mural producing symptoms due to intracavitary extension They usually involved the right heart and were polypoid in 20% The ventricles were involved as often as the atria Hemopericardium arrhythmias and inferior and superior vena caval obstruction were frequent

Tumors of the heart wall or valves such as angiomas hamartomas and nodular rhabdomyomas have been reported as incidental autopsy findings Benign pericardial tumors are rare but teratomas fibromas lipomas angiomas cysts and leiomyofibromas have been reported

Symptoms of intracavitary tumors are much oftener caused by other lesions Diagnosis depends on being aware of the possibility Signs of mitral stenosis not dating from birth in young children absence of difficulties until onset of intractable failure inconstant murmurs and episodes of syncope cyanosis or dyspnea without explanation except for change in position are all important clues

Differential diagnosis of tumors of the right heart include constrictive pericarditis tricuspid stenosis and insufficiency pericardial effusion superior vena caval syndrome and chronic congestive heart failure Angiocardiography makes the diagnosis of intracavitary tumor conclusive

Successful surgery of benign intrapericardial tumors has been reported only four time Six cases of intracardial tumors diagnosed during life have been reported Only one patient has survived surgery

Cardiovascular Manifestations of Collagen Diseases were reviewed by Matthew Taubenhaus Bernard Eisenstein and Alfred Pick[1] (Michael Reese Hosp) Since connective tissue is an intimate part of blood vessels and basement membranes in every organ of the body the function of most organs will be influenced by the state of the connective tissue The cardi

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Infiltrating the area with procaine the most effective therapy usually produces lasting relief Sometimes a second infiltration is necessary and occasionally a third Ethyl chloride spray may relieve an acute attack and the prompt occurrence of relief may aid in diagnosis When xiphoidalgia is associated with other disease control of the major disease may be followed by disappearance of xiphoidalgia The pain characteristically produces anxiety and the patient believes he has heart disease Even when procaine infiltration fail the pain will disappear spontaneously in weeks or months Xiphoidectomy is indicated only in patients with severe prolonged pain unresponsive to other therapy

The syndrome of hypersensitive xiphoid is probably commoner than generally appreciated It should be considered oftener in the differential diagnosis of pain in the chest or abdomen

Primary Tumors of the Heart Henry P Goldberg and Israel Steinberg[9] (New York Hosp—Cornell Med Center) reviewed the classifications diagnosis and treatment of cardiac tumors Incidence of primary tumors was rare only 0 0017% of 480 331 autopsies

Almost all intracavitary tumors originate in the atria Characteristically the syndrome mimics mitral or tricuspid valvular involvement without a history of rheumatic fever Exertional dyspnea is common and cardiac failure intractable Cardiac output is reduced angina may be present and systolic pressure is often low Fragmentation of the tumor may lead to emboli Other features are arrythmia syncope unexplained episodes of dyspnea cyanosis and orthopnea Symptoms and auscultatory signs may vary with change of position

In seven patients catheterization revealed obstructed outflow from the involved atria and elevated atrial pressure Definitive diagnosis depends on angiocardiography with characteristic filling defects in an enlarged atrium Mural thrombi do not produce filling defects and those due to a regurgitant stream from tricuspid insufficiency are transient An atrial obstructing thrombus (ball valve or pedunculated) has not been reported by angiocardiography but roentgen

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findings would be similar to those of intracavitary tumor Surgery should be considered for both conditions

Myxoma commonest intracavitary tumor has been reported in patients aged 3 months to 68 years It usually arises by a small pedicle from the atrial septum in the region of the fossa ovalis About 75% are in the left atrium

The other intracavitary tumors were sarcomas of all histologic types predominantly mural producing symptoms due to intracavitary extension They usually involved the right heart and were polypoid in 20% The ventricles were involved as often as the atria Hemopericardium arrhythmias and inferior and superior vena caval obstruction were frequent

Tumors of the heart wall or valves such as angiomas hamartomas and nodular rhabdomyomas have been reported as incidental autopsy findings Benign pericardial tumors are rare but teratomas fibromas lipomas angiomas cysts and leiomyofibromas have been reported

Symptoms of intracavitary tumors are much oftener caused by other lesions Diagnosis depends on being aware of the possibility Signs of mitral stenosis not dating from birth in young children absence of difficulties until onset of intractable failure inconstant murmurs and episodes of syncope cyanosis or dyspnea without explanation except for change in position are all important clues

Differential diagnosis of tumors of the right heart include constrictive pericarditis tricuspid stenosis and insufficiency pericardial effusion superior vena caval syndrome and chronic congestive heart failure Angiocardiography makes the diagnosis of intracavitary tumor conclusive

Successful surgery of benign intrapericardial tumors has been reported only four times Six cases of intr icardial tumors diagnosed during life have been reported Only one patient has survived surgery

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Cardiac enlargement without pericardial effusion is well known and probably due to myocardial involvement This can be followed with serial ECGs Discordant S T deviations from classic infarct patterns have been noted

Necrotizing angiitis is not a uniform disease Most conditions fall into one of five groups hypersensitivity angiitis allergic granulomatous angiitis rheumatic arteritis periarteritis nodosa or temporal arteritis Focal fibrinoid necrosis and inflammation of the vessel wall are common to all these groups Arteries and veins of any caliber may be involved Hypersensitivity angiitis the response to foreign protein and drugs affects small arteries arterioles venules and capillaries most commonly in the kidneys and heart The lesions start as fibrinoid necrosis in the subendothelial ground substance spread to the periphery and are accompanied by cellular infiltration of the wall and surrounding tissues Hypersensitivity angiitis is difficult to diagnose clinically because of its frequent association with other diseases for which the sensitizing agent was given The course is rapid and often fatal Skeletal muscle arteries are usually uninvolved and muscle biopsy is not helpful Fever is always present petechial and urticarial rashes are common as is nephritis with hematuria and azotemia Congestive failure may occur from multiple miliary myocardial infarcts

Allergic granulomatous angiitis is associated with asthma fever and eosinophilia Vascular occlusion and infarction occur in multiple organs Extravascular lesions consist of nodular granulomas with giant cells Aneurysm of mesenteric vessels is common Subcutaneous nodules in the skin verify the diagnosis by biopsy

Rheumatic angiitis affects the small arteries and occasionally the veins of the lung and heart and less commonly of the mesentery The clinical course is that of fulminating rheumatic fever

Periarteritis nodosa is the most common form of necrotizing angiitis involving the small and medium sized coronary mesenteric renal and muscular arteries Splenic and pulmonary vessels are usually spared Clinical manifestations are protean due to focal ischemia by arterial occlusion in any organ of the body Cardiac enlargement retinopathy and congestive failure are secondary to hypertension and renal

nal pathologic changes in collagen disease are fibrinoid degeneration ground substance and fiber formation changes and inflammation The cardiovascular system is involved to a varying degree in all the entities that are considered collagen diseases

Systemic lupus erythematosus may be present for months or years before cardiovascular abnormalities are clinically detected Clinical signs are fever weight loss typical skin lesions lymphadenopathy and splenomegaly arthralgias or arthritis polyserositis pneumonitis and anemia or central nervous system disorders Laboratory tests may show false positive serologic test for syphilis normochromic anemia leukopenia thrombocytopenia hyperglobulinemia and a rapid sedimentation rate A positive L E test is present in about 75%

The arteries and arterioles of almost any organ may undergo subendothelial fibrinoid necrosis with proliferation of fibroblasts Swelling of the wall may narrow the lumen and impair blood flow In the spleen and kidneys the pathology is characteristic with sclerosis of collagen fibers around central and penicillate arteries of the spleen and wire loop appearance of glomerular arterioles The pericardium and epicardium usually show fibrinoid necrosis Fibrinoid necrosis of supportive structures and vessels in the myocardium usually causes secondary degeneration of muscle fibers and focal fibrosis Degeneration of the ground substance and increase of fibrinoid material may cause such swelling that actual verrucae are formed most frequently on the tricuspid valve on both sides of the cusps Severe valvular deformity does not occur

Clinical signs of arteritis are protean Raynaud s phenomenon convulsions hemiplegia peripheral neuritis retinal hemorrhages and exudates intestinal hemorrhages pancreatitis renal vascular involvement with albuminuria hematuria and cylindruria azotemia and myocardial infarction have all resulted from lupus angiitis of the associated vessels Pericarditis has been reported in as high as 45% of patients with lupus erythematosus

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Dermatomyositis involves predominantly the skeletal muscle and skin with weakness tenderness and swelling in the shoulder and pelvic girdles and extremities Many patients have dysphagia Vascular changes consist in fibrinoid necrosis and deposition of hyalinized material in the media of arterioles Muscle fibers show fragmentation loss of striation and vacuolization The nuclei are irregular in size and shape Interstitial tissue shows swelling edema and inflammatory infiltrates Myocardial changes resemble the changes in the skeletal muscle but are less severe

Clinical vascular manifestations are not prominent except for Raynaud s phenomenon Renal impairment has not been observed The mo t common cardiac manifestation is tachycardia out of proportion to temperature elevation Dermatomyositis is a definite entity but clinically overlaps scleroderma The resemblance to systemic lupus erythematosus is superficial

The serum sickness syndrome is present most frequently after penicillin therapy The onset is sudden after a latent period of varying duration The most prominent signs are urticaria joint swelling and fever The intima and adventitia of arteries and veins are edematou and there is proliferation of fibroblasts endothelial cells plasma cells and lymphocytes in the endocardium myocardium and pericardium The histologic appearance of the vessels may be indistingui hable from hypersen itivity angiitis but the cour e is usually benign

Corticosteroids and ACTH are beneficial in sy temic lupus erythematosus and in necrotizing angiitis They are of questionable benefit in progressive systemic sclerosis In dermatomyositis general symptoms may be improved but information concerning cardiovascular improvement is insufficient Serum sickness is a self limited disease but the clinical course may be shortened by steroid therapy

Pitfalls in Care of Cardiacs Samuel A Levine[2] (Harvard Med School) reviewed errors of omission and commission frequently made in the general practice of cardiology

Diagnosis is the most important pha e A frequent error i the quick assumption that breathlessness is due to heart failure Functional dyspnea especially the sighing type

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involvement Electrocardiograms may reveal typical evolution of pericarditis myocarditis or confluent myocardial necrosis but will not differentiate the various collagen diseases

Temporal arteritis is usually restricted to cranial arteries in older individuals The larger muscular arteries are involved proximal to their bifurcation and the aorta as well as smaller vessels may show the characteristic lesions microscopically The lesion is characterized by granulomatous nodules surrounded by inflammatory cells and foreign body giant cells

In general necrotizing angiitis is a primary disease of the vessel wall The narrowed lumens diminish blood flow and organ function is impaired Pleuritis pericarditis synovitis myocarditis and polyarthritis cannot be explained by ischemia and infarction but the same factor that causes the vascular lesion probably attacks serous membranes

The outstanding manifestation of progressive systemic sclerosis (scleroderma) is a generalized increase in collagen fibers The skin of the face extremities and trunk are thickened and inelastic The esophagus is commonly involved the small bowel occasionally and the colon rarely Involvement of the joints may be similar to rheumatoid arthritis and skeletal muscle atrophy may resemble the lesion of dermatomyositis Pulmonary involvement is common with fibrosis of peribronchial and alveolar interstitial tissues thickening and destruction of alveolar walls and cyst formation

Vascular manifestations are extensive The vessel wall is thickened by perivascular fibrosis and the adventitia infiltrated with inflammatory cells Intimal proliferation may occlude the lumen The initial renal lesion is intimal thickening in the intralobular arteries causing gradual ischemic atrophy of portions of the renal cortex Fibrinoid necrosis of the distal part of the intralobular arteries and of the afferent arterioles then occurs and glomerular fibrosis may follow

Clinically Raynaud s phenomenon is prevalent in scleroderma Renal involvement is usually not apparent until a late stage Pulmonary involvement is manifested by hypoxia carbon dioxide retention emphysema pulmonary hypertension and polycythemia in protracted cases Cardiac lesions of patchy interstitial fibrosis in the myocardium may lead to congestive failure ECG changes and precordial pain Collagen may actually replace cardiac muscle

to the back of the neck This peculiar localization is rare in coronary artery disease

Accurate anatomic diagnosis of valvular disease has now become important since surgery is available The main challenge is recognition of mitral stenosis Helpful features are diastolic and/or presystolic apical rumble calcification of the mitral valve accentuated apical first sound opening snap accentuated and split pulmonary second sound broad flat topped and notched P waves in the limb leads of the electrocardiogram right ventricular hypertrophy dilated left auricle and main pulmonary artery in x ray A history of rheumatic fever or chorea is helpful indirectly Systolic murmurs and various arrhythmias have occurred in the absence of significant organic disease Other evidence of organic pathology is required

Hypertensive valvular or coronary heart disease may be present for many years without failure and congestive symptoms may never develop Mild prohibitions may be justified but digitalis is useless and often makes the patient mentally and physically worse The only reliable sign of failure by examination of the heart is diastolic gallop Extracardiac signs and a history of unaccustomed dyspnea are necessary for the diagnosis Increased venous pressure in the absence of local venous obstruction is fairly reliable for right sided failure and prolonged circulation time is good evidence of left ventricular failure or pulmonary congestion X ray of the lung may show congestion and vital capacity measurement may indicate the presence and degree of left sided failure Peripheral edema hepatomegaly pulmonary rales or pleural fluid may be due to causes other than congestive failure and must be properly evaluated

An increasing number of patients have curable or reversible heart disease These include beriberi heart disease masked hyperthyroidism constrictive pericarditis severe anemia congenital cardiac lesions amenable to surgery arteriovenous aneurysm and occasionally arrhythmia in otherwise healthy hearts These conditions must be recognized to be effectively treated

After congestive failure has been established and the possibility of reversible pathology eliminated appropriate digitalis low salt diet diuretics and rest should be instituted

should be recognized easily because such patients are normal physically They claim insufficient air intake when actually they are overventilated and seem short of breath at rest without cause When a patient with organic heart disease is breathless at rest he is obviously sick with ample evidence of his disease Breathlessness of bronchial or emphysematous origin is often confused with that due to cardiac disease The character of the breath sounds prolonged expiration with squeaking disseminated rales emphysematous appearance on inspection and x ray and normal heart size all are differentiating features Such patients are frequently given digitalis on the erroneous diagnosis of heart failure Discontinuing digitalis and giving such medications as ephedrine directed at the pulmonary problem is often rewarding

Another error is the interpretation of various forms of chest discomfort Angina may be present even though the most careful physical examination shows normality Effort tests and attempts to reproduce pain occasionally are helpful If carotid massage slows the heart rate and abolishes a typical attack of pain even though only temporarily the diagnosis of angina is fairly certain Symptoms characteristic of angina have been ascribed to hiatus hernia and biliary tract disease when these have been demonstrated The patient may also have coronary disease and the symptoms must be fully appraised With both biliary and coronary disease present angina has not disappeared after surgery although occasionally it has been improved

A more important diagnostic pitfall is the distinction between coronary thrombosis and pulmonary embolism which may be difficult Electrocardiographic changes occur in both and may be similar Occasionally patients with pulmonary embolism breathe in quick gasps lifting the clavicles and widening the mouth laterally yet the breath sounds are decreased The sequence of accident thrombophlebitis (whether or not detected) and pulmonary embolism is so frequent that the diagnosis should be considered first in patients in collapse after an injury

Acute dissection of the aorta can often be differentiated by an increase in the size of the aorta in x ray In a few patients the pain is severe and piercing from the center of the throat

8 and previous myocardial infarct in 7 Cerebrovascular occlusion was caused by thrombus in 27 and by embolus in 8 3 of whom were convalescing from acute myocardial infarct and 5 with rheumatic heart disease and chronic auricular fibrillation Signs and symptoms were severe in 32 Eight were disoriented or semicomatose 18 had marked right sided hemiparesis conjugate deviation of the eyes and clouded consciousness 4 had flaccid paralysis of the left extremities and 8 had left sided hemiparesis but in 3 of these involvement was mild

Usually 300 mg cortisone was given orally in divided doses on each of the first two days and was progressively decreased to 50 mg daily through the third week Patients who were comatose or had difficulty in swallowing were treated parenterally In 22 patients steroid therapy was started within 24 hours of the cerebrovascular accident and in all patients within 48 hours

Dramatic clinical improvement was noted within 24 hours of therapy in 21 Paralytic signs and symptoms were ameliorated and mental emotional sensory and psychomotor status improved Conjugate deviation of the eyes incoherent speech dysarthria and aphasia rapidly cleared Greatest effects were noted among the somnolent stuporous mentally depressed or apathetic 19 such patients overnight becoming alert and interested in their progress Active rehabilitative measures were easily instituted after one or two days treatment because of rapid recovery from acute mental disturbances improved motivation psychomotor stimulation and sense of well being In four patients with complete flaccid paralysis of the involved extremities motor power did not improve though the psyche was unmistakably benefited

After a week of therapy cortisone was discontinued in three patients Paresis increased in two of these but when cortisone was readministered motor power again improved No such rebound was observed in any patient treated for the full three weeks At the end of three weeks of cortisone therapy 27 had almost completely recovered neurologically Residua consisted of mild to moderate weakness in the hand grip mild footdrop lower facial paresis and minor speech and deglutition defects

Cortisone is a valuable addition to the therapy of acute

Therapeutic pitfalls are few The most common is refractoriness to mercurial diuretics usually due to electrolyte abnormalities induced by the diuretics Replenishing chlorides and occasionally potassium will restore a responsive state In some cases with massive anasarca mercurials intravenously *especially if followed by aminophylline may initiate* diuresis that cannot be obtained by intramuscular injection Removal of ascites or of massive edema in the legs with Southey tubes may allow diuretics to become effective again

Many patients with congestive failure may be helped by phlebotomy if they are not hypotensive or by correction of hydrothorax Most patients with cardiac disease including acute coronary thrombosis will be more comfortable in a *chair with their feet down than in bed all day* particularly when dyspnea and pulmonary congestion are the main problems The only contraindications are shock lightheadedness or extreme weakness

The incidence of digitalis intoxication has increased with the use of pure glycosides Current cardiac therapy with low sodium intake and frequent use of mercurials has depleted the body potassium in many patients and doses of digitalis which formerly were nontoxic become toxic One result may be a peculiar arrhythmia paroxysmal tachycardia with block often mistaken for auricular tachycardia auricular *flutter or fibrillation or sinus tachycardia and treated* with more digitalis In this event the drug should be omitted promptly and pronestyl® or potassium chloride administered intravenously if necessary

Before a patient with heart disease is treated the physician must determine whether organic heart disease or congestive failure is present and finally whether the form of heart disease is reversible

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CEREBRAL VASCULAR DISEASE

Cortisone in Immediate Therapy of Apoplectic Stroke was given to 35 patients aged 40 74 (average 60 2) by Henry I Russek Allen S Russek and Burton L Zohman[3] (New York) Hypertension was present in 24 angina pectoris in

(3) J A M A 159 10 105 Sept 10 1955

tients with cerebrovascular disorders Intracranial angiography is indicated when possibly surgery after subarachnoid hemorrhage requires precise diagnosis when effects of arterial occlusion are indistinguishable from intracranial tumor and for exact localization of expansile intracranial lesions Vascular contrast studies are precluded when differentiation is only academic when the patient is extremely old or has advanced arteriosclerosis or hypertension heart failure uremia or a recent severe infarctive stroke An EEG is valuable in differential diagnosis of vascular disorders of the brain Residual EEG abnormalities following cerebral infarction are common in the ipsilateral temporal area Relatively constant production of irregular slow waves tends to distinguish infarction from infiltrative malignant neoplasm Minor irregular and slow spike activity from the anterior temporal leads frequent in elderly patients probably results from small infarction in the tip of the temporal lobe

Therapeutic use of stellate nerve block in cerebral vasospasm is a subject of neurologic debate Since collateral channels may be enhanced by vasodilation and temporarily anoxic neurones in border zones of ischemia are capable of revival there is no reason to withhold stellate block from the patient with a recent nonhemorrhagic stroke even though total cerebral blood flow is not increased Dramatic results are achieved in 3 5% of patients and moderate but definite response in an additional 30%

The clinical syndrome in patients who are potential candidates for intracranial surgery after spontaneous cerebral hemorrhage is (1) initial verified brain hemorrhage with coma or stupor (2) restoration of consciousness in the presence of lateralizing neurologic signs and (3) subsequent loss of alert behavior with other signs of increasing intracranial pressure Ventriculographic compression or displacement of major cerebral arteries in angiograms are good neuroradiologic localizing procedures Results of surgery are good but further complications of hypertensive cardiovascular disease usually appear later Operative intervention has nothing to offer the usual intraventricular flooding hypertensive blowout

The principal means of prevention of initial or recurrent cerebral embolization is anticoagulant therapy Variability

cerebral thrombosis or embolism It offers a dynamic approach to limiting the assault of the disease No significant untoward effects from cortisone were noted

Sympathetic Block in Apoplexy Geza de Takats[4] (St Luke s Hosp Chicago) reports results in 55 patients given 1 10 cervical sympathetic blocks as part of an emergency treatment for apoplexy 14 had emboli and 41 infarcts Injections were not used for other apoplectic patients with massive hemorrhage subarachnoid hemorrhage cerebral venous *thrombosis and brain tumor A little over half of the 55 pa*tients (and 65% of 533 reported on in the literature) improved immediately Since improvement in the present series was noted within 15 30 minutes of injection it cannot be attributed to gradual regression of neurologic symptoms When improvement did not occur despite a definite Horner s syndrome injections were discontinued If improvement was noted injections were continued twice a day one for each side until the patient s condition became stationary The block failed in 23 patients Best results have been obtained in early cases and no patient has shown clearcut improvement if the block was given 48 hours or more after the stroke

For the block 10 cc of 1% procaine without epinephrine is *injected via a lateral or anterior approach at the level of the* sixth cervical transverse process Phenol is never injected at this level No untoward symptoms have occurred

Almost all apoplexies are due to cerebral infarcts ischemic or hemorrhagic due to emboli thrombi or cerebrovascular insufficiency in cerebral arteriosclerosis As long as these lesions create a perifocal edema sympathetic block seems worthy of further trial At present there is no way of selecting suitable cases but the technic is harmless and results when obtained are gratifying

• [Carbon dioxide is a cerebral vasodilator In some patients with apoplexy the inhalation of 5 10% carbon dioxide as tolerated by the respiration *may produce temporary improvement in neurologic* symptoms It appears that such patients are particularly likely to be benefited by a sympathetic block —Ed]

Recent Advances in Investigation and Management of Cerebrovascular Disease are reviewed by James Peter Murphy[5] (George Washington Univ) Ventriculography has been superseded largely by angiographic examination of pa

(4) S rg ry 39 915 927 N embe 1955
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elevated blood pressure usually clears the sensorium stops seizures and releases vasoconstriction Careful intravenous titration with various ganglion blocking agents is advised Magnesium sulfate is used in control of eclamptic convulsions Antiepileptic drugs should be used in combined chronic hypertensive brain disease abnormal EEG and paroxysmal neurologic symptoms

Histamine cautiously administered often helps overcome effects of cerebral arteriosclerosis (little strokes) Sustained anticoagulant therapy has been suggested when insufficiency of the basilar artery is suspected Metrazol® orally is recommended for improvement in mood orientation industry and co operation in patients with severe cerebral arteriosclerosis

In general management the ideal parenteral solution is 2 5% glucose in 0 42% saline with reference to intracranial pressure alone this causes little disturbance of cerebrospinal fluid pressure and does not predispose to edema If hypernatremia develops saline solutions are withheld until serum sodium returns to normal Physiotherapy is beneficial in helping restore the hemiplegic patient to normal to a working level or simply to a stage of self care Learning on both paretic and nonparetic sides of the body occurs chiefly in the first two months after brain injury

Clinical Localization of Intracranial Aneurysms and Vascular Anomalies is reviewed by A Earl Walker[6] (Johns Hopkins Univ) in 285 aneurysmal tumors Subarachnoid hemorrhage can often be diagnosed by history alone and confirmed by lumbar puncture Further management depends on accurate localization and precise diagnosis of the lesion

Aneurysms of the internal carotid artery below the anterior clinoid process lie almost entirely within the cavernous sinus When ruptured they produce a carotid cavernous fistula rarely epistaxis and subarachnoid hemorrhage only if the lesion extends above the clinoid process Of six patients five had diplopia with or without ptosis and one pain as the initial symptom In one patient with combined infra and supraclinoid aneurysm unilateral blindness was the first symptom The cranial nerves within the cavernous sinus

(6) Neu log 6 79 90 F bru y 1956

of blood coagulation in other types of brain stroke precludes routine use of anticoagulants except in suspected incipient thrombosis of the internal carotid or basilar arteries, extension of clotting from an arterial aneurysm treated by ligation of the main carotid vessel or migratory thrombophlebitis with intracranial involvement. Stellate block is the procedure of choice in sudden cerebral embolism; persistent peripheral angiospasm has been proved to follow major cerebral arterial embolic occlusion.

In cerebral thrombosis or infarction, stellate block is of possible benefit if angiospasm on the periphery of the lesion is significant. Addition of 5-7% CO_2 to inhaled oxygen may aid in development of collateral cerebral circulation. Cortisone or hydrocortisone aids recovery from hemiplegia after cerebral infarction. Nicotinic acid (300 mg. three times daily) seems particularly beneficial after occlusion of the posterior inferior cerebellar artery.

For subarachnoid hemorrhage from intracranial aneurysm, proximal ligation of the cervical carotid artery is preferred in control of aneurysms arising from the terminal intracranial carotid artery or its proximal branches, provided that preoperative occlusion demonstrates ability of the brain to survive when inflow from one carotid has been sacrificed. Peripheral aneurysmal lesions may be dealt with as surgical judgment dictates. Decision is difficult, since cervical carotid ligation reduces pressure in intracranial derivative vessels of small size almost as much as does clipping of the parent branch vessel. The assumption that reduction of arterial pressure head by cervical carotid ligation causes local thrombosis of the aneurysm is supported by long-term follow-up in reported series.

In arteriovenous malformations, direct approach to the lesion is advocated. However, symptomatic response may be obtained by an indirect surgical approach, such as carotid ligation, when actual removal of abnormal blood vessels might paralyze or kill. Epilepsy, often symptomatic of these lesions, is not eliminated by any operation.

In intracranial thrombophlebitis and venous thrombosis, anticoagulants are ideal therapy. Antibiotics are also indicated in large dosage if inflammation is of bacterial origin.

In management of hypertensive encephalopathy, lowering

does not present a classic clinical picture but hemiparesis without cranial nerve involvement suggests this diagnosis Aneurysms of the middle cerebral artery cannot be diagnosed before rupture but after rupture sudden loss of consciousness occasional seizures hemiparesis signs of subarachnoid hemorrhage and history of headaches are suggestive

In supratentorial cerebral vascular anomalies 90% of patients have symptoms before age 40 the commonest being epilepsy localized jacksonian seizures with lesions of the central region of the cortex and focal manifestations corresponding to appropriate cortical areas The next commonest symptom was hemiparesis Manifestations of subarachnoid hemorrhage were present in 14 of 64 patients Clinical findings associated with subtentorial vascular anomalies are not characteristic and are those of any space occupying lesion in the posterior fossa

Syndrome of Intermittent Insufficiency of Basilar Arterial System is reported in eight patients by Robert G Siekert and Clark H Millikan[7] (Mayo Clinic and Found) Transient episodes of focal neurologic abnormalities in middle or older age groups have been variously attributed to so called vasospasm or small strokes One group of patients has transient episodes presumably due to insufficient blood flow through the basilar arterial system These periodic phenomena are probably commoner than generally believed They are often present in the history of patients who finally have the basilar artery occluded by thrombosis

The manifold symptoms include weakness of the limbs visual or oculorotatory abnormalities pseudobulbar or bulbar phenomena numbness and miscellaneous symptoms Each can be explained by poor blood flow in the area supplied by the basilar artery They form a pattern explained by abnormalities in this field alone

The study showed that weakness or poor use of a limb consisted of monoparesis hemiparesis or quadriparesis Hemiparesis on one side in one attack and on the other in a different attack was highly suggestive of basilar arterial insufficiency

Ophthalmologic abnormalities were visual dimness and oculorotatory trouble Homonymous hemianopsia or bilater

(7) Neu logy 5 6 5-630 Septembe 1955

were involved and in two patients the second cranial nerve also The unruptured infraclinoid aneurysm typically presents as third nerve palsy and slight involvement of the upper one or two divisions of the trigeminal nerve Other lesions in the same region may produce similar pictures but severe pain is commoner with infraclinoid aneurysms

Most carotid cavernous fistulas are of traumatic origin and occur immediately a week or months after injury A bruit usually *the first manifestation may be present* for weeks before exophthalmus the cardinal symptom appears It is usually unilateral in the ipsilateral eye bilateral in about 10% and rarely in the contralateral eye alone Pulsation of the globe is present in almost 90% often with a thrill over the orbit or the engorged vessels of the forehead Compression of the ipsilateral carotid artery usually diminishes or abolishes the bruit Involvement of the optic nerve or paresis of extraocular movements is common

In supraclinoid aneurysms before and after rupture commonest earliest symptom was headache or pain in the head present as long as 14 years before *frank rupture* The next commonest symptoms were failing vision and hemiplegia Of the 71 patients 46 had subarachnoid hemorrhage one half of these had no premonitory symptoms Paralysis of the *third cranial nerve on the side of the aneurysm was present* in 40 patients coma without premonition was the first manifestation in 6 There is no pathognomonic clinical picture of supraclinoid aneurysms of the internal carotid artery Roentgenographic evidence of bony destruction of the *sella* turcica including the anterior clinoid processes confirms diagnosis

Of 37 patients with aneurysms of the anterior cerebral arteries or anterior communicating artery 11 had no premonitory symptoms before rupture and coma The commonest premonitory symptom was headache of a nondescript nature in 15 patients Other symptoms were visual loss in three photophobia in one and epilepsy in two Diagnosis was made at time of rupture in *27* patients 20 of whom were in coma A comatose patient with a history of visual impairment and no *oculomotor* palsy is likely to have an aneurysm of the anterior carotid artery

Aneurysms of the first part of the middle cerebral artery

of arteriosclerosis local and systemic blood pressure cardiac disease vasospasm blood viscosity and the tendency to thrombus formation

In seven patients with intermittent insufficiency of the internal carotid artery the symptoms in all the attacks had been remarkably similar With the administration of dicumarol[8] the intermittent cerebral symptoms and signs did not recur while the prothrombin time was sufficiently prolonged None of the patients developed cerebral infarction

The number who would have developed infarction if anticoagulants had not been given is unknown and the correct duration of such treatment is not known although long term anticoagulant therapy is advised

PERIPHERAL VASCULAR DISEASE

Aortic Dissection (Dissecting Hematoma Dissecting Aneurysm of Aorta) is reviewed by Howard B Burchell[9] (Mayo Clinic) in 40 autopsies This condition should not be called dissecting aneurysm as it is not aneurysmal but a dissecting hematoma with progressive splitting of the medial layer of the aorta Syphilis is not etiologically related and the lesions of chronic syphilis prevent or limit aortic dissection

Increasing incidence of aortic dissection is probably related to an aging population Length of survival is generally directly proportional to the distance of the intimal tear from the aortic valve *The primary intimal tear was in the ascend*ing aorta in about 50% of cases in the arch in about 30% and in the descending portion in 20% The dissection involved the ascending aorta in 70% the arch in 90% and the descending aorta in 80%

Medial degeneration is the *sine qua non* of spontaneous aortic dissection The histology represents a metabolic end effect to which hypertension in some unknown manner contributes In young adults degenerative medial change is mainly in the elastica Atherosclerosis is not a cause of aortic dissection though the latter occurs in atherosclerotic aortas Rarely a mycotic aneurysm may initiate dissection All di

(9) C 1 on 12 1068 1079 D mbe 1955

al homonymous hemianopsia was frequently present Diplopia was less frequent Pseudobulbar or bulbar phenomena of dysphagia and dysarthria were common but not necessarily simultaneous

Numbness may appear in a limb or one side of the face or body Characteristically the numbness alternated from side to side in different attacks The miscellaneous symptoms included vertigo and confusion without tinnitus or loss of hearing Vertigo may be associated with nausea or vomiting

The occurrence of these symptoms in sharply episodic form and the pattern evolved appear to be due to temporary ischemia within the field of the basilar artery The authors suggest the term intermittent insufficiency of the basilar arterial system

• [Recently it has been recognized that insufficiency or thrombosis of the basilar arterial system is a common finding It seems likely that long term anticoagulant therapy may be of value in such patients as well as in those described in the following abstract—Ed]

Studies in Cerebrovascular Disease V Use of Anticoagulant Drugs in Treatment of Intermittent Insufficiency of Internal Carotid Arterial System According to Clark H Millikan *Robert G Siekert and Richard M Shick*[8] when thrombosis occurs the quantity and severity of infarction depend on the adequacy and speed of development of collateral circulation Once extensive infarction has occurred in the central nervous system therapy directed to the vascular system probably will be ineffective Effective therapy depends on prevention of thrombosis

The present concept of the pathogenesis of the attacks is as follows A soft thrombus forms on diseased endothelium in the internal carotid artery It may alter the blood flow or break from its source fragment and be carried away More likely the newly formed clot lodges for a few minutes at a branch in the vessels producing symptoms and then fragments and is carried away This would explain the rapid onset and short *duration of the attacks their remarkable* constancy the absence of residual neurologic signs and the cessation of attacks during adequate anticoagulant therapy This concept of course does not explain all cerebral infarctions Cerebral infarction may result from the interplay of many variable factors including the degree and extent

(8) P oc Staff Meet M y Cl 30 578 586 Nov 30 1955

ther follow up Plastic repair rejoining the distal portion and reconstructing the aorta apparently was successful in four of six patients Ideally early surgical treatment with replacement of a limited aortic dissection by graft might be possible in selected patients particularly if the lesion is in the distal part of the aortic arch or in the descending thoracic aorta

[Patients with dissecting aneurysm may occasionally display pulsation of the right sternoclavicular joint or a friction rub synchronous with the heart beat in the upper interspaces in the parasternal regions They likewise may display intermittent neurologic abnormalities in the legs such as temporary disturbances of sensation or of reflexes However the manifestations described by the authors are the more common ones The recognition of aortic dissection i becoming increasingly important as operative technics are being rapidly improved —Ed]

Unusual Manifestations of Coarctation of the Aorta are reported by George C Griffith Robert W Oblath and John C Jones[1] (Los Angeles) in a study of 118 established cases Almost half the patients presented unusual findings

In acyanotic infants under age 6 weeks heart failure is usually due to infantile type coarctation or to aortic stenosis The adult type coarctation in which constriction is usually limited to a small segment of the aorta is most commonly seen by the clinician The findings include reduced or absent pulsations in the abdominal aorta and femoral arteries associated with hypertension in the upper extremities a loud rough precordial systolic murmur at the base of the heart shortly after the first sound and without a thrill collateral arterial circulation hypertrophy of the left ventricle and dilation of the ascending aorta a defect or break in the continuity of the aortic outline in the left anterior oblique position by x ray an absent aortic knob bilateral notching of lateral and posterior portions of the ribs and abnormal asynchronism between the radial and femoral arteries

Unusual findings on clinical examination include diminished or absent radial pulse on one side Absence of the left carotid and left subclavian pulses or reduced pulsation in these vessels suggests coarctation between them Rarely the coarctation may be limited to the left subclavian artery alone Another unusual finding is unilateral rib notching on the right side of the body This confirms the location of the coarctation between the left carotid and left subclavian Pul

(1) C cul t 12 1080 1083 Dec mb 1955

secting hematomas begin with hemorrhage from vasa vasorum with secondary intimal rupture Associated systemic problems include pregnancy coarctation aortic valvular disease and possibly myxedema Almost all patients have hypertension either recent or severe and progressive

The clinical picture is protean Characteristically pain is severe and unrelenting moving from one region to another particularly from thorax to back to abdomen to extremities It may occur first in the face ear or neck or be entirely absent Syncope or shock may be present but usually the pressures are very high though the patient may be cold and sweaty with feeble pulse A double bruit may be present at the aortic area and arterial pulsations may or may not be unequal in the extremities Paraplegia or hemiplegia may be the main features or abdominal symptoms with pain distention and urge to defecate may predominate Hoarseness and Horner s syndrome have occurred fever and leukocytosis may occur early and if bleeding is external progressive anemia may be noted Myocardial infarction is usually suspected especially when the history includes anginal pain or previous myocardial infarction Acute pancreatitis or mesenteric thrombosis may be suspected

Besides suspecting or even diagnosing a dissecting aorta the extent should be appraised and the site of the intimal tear estimated This may become increasingly important as surgical therapy progresses Simultaneous pain in the back and epigastrium favors the aortic arch or just beyond the left subclavian as site of dissection A pronounced and persistent murmur of aortic insufficiency previously not heard makes it likely the tear is within a few centimeters of the aortic valve In chronic dissecting hematoma x ray may assess the limits of the lesion

Anticoagulants are usually contraindicated because of the danger of facilitating a leak at a site of an external near rupture These drugs probably do not influence progression of the hematoma per se Ganglionic blocking antihypertensive agents have not been universally successful after recovery from the acute phase A re entry opening in the dissected femoral artery has been reported to relieve an ischemic limb The involved aorta has been wrapped with cellophane in two patients Both lived at least two years but were lost to fur

Multiple aberrant systemic arteries may be present and their accidental incision during surgery must be avoided In one of the two cases a bronchial adenoma of the oncocyte carcinoid type was found in the cyst wall Such tumors are potentially malignant

Careful study indicates contrary to previous reports that the aberrant arteries differ strikingly from pulmonary arteries They are thicker and contain more muscle tissue and the media contains long plump elastic fibers in concentric lamellas The aberrant vessels resemble systemic elastic or hybrid arteries capable of withstanding high pressures Whereas the aberrant arteries showed no degenerative stigma arteries and veins showed advanced sclerosis in the affected lung segment and in the unaffected areas early arteriosclerosis when surgically resected

Portal Venography Anatomic and Physiologic Considerations in Interpretation are discussed by Francis F Ruzicka Jr Guenther A Doehner and Louis M Rousselot[3] (New York) Percutaneous needle insertion into the spleen with injection of contrast medium into the sinuses is the most popular method At laparotomy injection of a cannulized portal vein is useful

Anatomic and physiologic data derived from portal venograms include existence or nonexistence of portal system vessels their position size and relation presence and extent of varices and other intrinsic vascular lesions extravascular lesions that may displace deform or obstruct segments and demonstration of collaterals The portal venogram thus may provide evidence of portal obstruction or hypertension

The normal portagram in the living subject reveals only vessels between site of injection and the liver Visualization of veins not in the direct course to the liver indicates portal obstruction and generally *means that portal blood flow is reversed* Complete thrombosis of portal system veins is rare and incomplete thrombosis is difficult to recognize Diminished arborization of the portal tree and distorted intrahepatic branches have been noted in cirrhosis Demonstration of collateral veins definitely indicates portal obstruction and suggests portal hypertension The collateral vein most frequently encountered was the coronary esophageal A transhepatic collateral vein arising in the liver and joining the

(3) Am J Dig i D 1 3 0 1956

sations below the diaphragm constitute a third unusual finding Absence of abdominal aortic pulsation and presence of propulsion pulse in the femoral arteries suggest atresia of the distal aorta When coarctation occurs below the diaphragm it is usually at or below the renal arteries

The constriction may be visualized by angiocardiography or preferably by aortography Accurate localization estimates of the length of stenosis and of the distance between the left subclavian artery and the constriction may be determined by this method

Of the 118 patients 62 had uncomplicated coarctation with classic symptoms and surgery was without incident 28 of the 118 died 6 soon after birth 8 before age 3 months 7 before surgery could be performed (all older than 12 months) 3 during surgery and 4 postoperatively Of 18 patients with complications 9 had a coexisting patent ductus arteriosus Three patients were denied surgery because of excessive atherosclerosis in the aorta

Patients with classic signs of coarctation of the aorta should have resection of the coarcted area A commonly associated defect is patent ductus arteriosus which acts as a compensatory *mechanism in severe coarctation Surgery* of coarctation in presence of mitral or aortic stenosis is usually fatal The head should always be carefully auscultated because *congenital aneurysm of cerebral vessels is frequently* associated with coarctation of the aorta

Vascular Changes in Bronchopulmonary Sequestration Observations in Two Cases with Multiple Accessory Systemic Arteries are reported by Martin Bergmann and I Jerome Flance (St Louis) Most aberrant vessels to the lungs originate from the descending aorta near the diaphragm When they originate from other large systemic arteries cardiovascular anomalies are usually also present The lung supplied may be otherwise normal but usually the area contains cysts or cystic bronchiectasis Frequently the dilated *bronchi* have *no demonstrable communication* with the bronchial tree (intra lobar sequestration) These accessory systemic vessels and associated abnormalities are congenital Clinical *symptoms or signs are absent unless* secondary infection occurs in the cystic lung

(2) J Thora c S rg 31 199 210 F b uary 1956

A walking program is recommended patients being urged to walk to pain tolerance at least four times daily This provides the most effective physiologic stimulus for the development of collateral circulation in the ischemic zone and is a simple and safe program Meticulous care of the feet is imperative Temperature extremes and mechanical trauma must be avoided

Therapy in Intermittent Claudication Julius Pomeranze Raymond J Gadek Ernest R Pitman and Siegfried Scherl[5] treated 24 patients who had diabetes mellitus and intermittent claudication or nocturnal muscle cramps with arlidin an arylakyl vasodilator of the adrenaline ephedrine series Its formula is 1 (p hydroxyphenyl) 2 (1 methyl 3 phenyl propylamino) propanol

Experimentally the acute toxicity of arlidin has been found to be low with a wide margin of safety In the mouse the acute LD_{50} was 40 mg/kg intravenously and 200 mg/kg subcutaneously and both oral and parenteral administration produced peripheral vasodilatation In perfused guinea pig hearts doses as low as 100 µg increased coronary flow amplitude and rate of contraction Flow in the failing guinea pig heart was doubled and the rate increased Similar results were obtained in the isolated perfused rabbit heart Local anesthetic activity was demonstrated in the conjunctiva of the rabbit and marked and prolonged local vasodilatation was produced by intradermal injection in the ear of the rabbit

All 24 patients were given arlidin orally 3 12 mg three times daily *Most patients felt a tingling and warmth* 10 minutes after taking the drug The disappearance of night cramps or a threefold increase in the distance a patient could walk conditions being similar was considered a good response Nineteen patients had a good response

Long Term Treatment of Some Arteriopathies with Tromexan® At some time in their development chronic arteriopathies manifest arterial thrombosis If the thrombosis develops slowly an adequate collateral circulation may be established but if rapidly developed the limb may be endangered Carlos M Castro and German Stritzler[6] (Buenos

(5) A gi I gy 6 71 75 J 1955
(6) Ib d pp 442 461 O t be 1955

coronary vein retroperitoneal plexus or adrenorenal veins was present in over 50% of the authors venograms made in living subjects

Intermittent Claudication is discussed by Stanford Wessler[4] (Harvard Med School) Diagnosis depends on history of pain or paresthesia in the foot calf or thigh produced by physical exertion and promptly relieved by cessation of activity without change of position of the affected part It never occurs in the legs from standing reclining or sitting and is not related to muscle cramps in bed Atheromatosis is the most common cause Pain results from muscular ischemia Arterial occlusive disease provides a blood supply inadequate for actively contracting but sufficient for resting muscle

Pedal pulses are absent *This finding is so constant that* diagnosis must always be doubted if pulses are present Other pathology such as neuritis or arthritis must be excluded as cause of pain The oscillometer is over rated as an aid in diagnosis because of the many variables introduced Its main value is confirming absence of palpable pulses and demonstrating a difference in pulsatile flow in extremities when pulses *are absent in both*

Calcification in the walls of atherosclerotic vessels is not significant The effects depend on narrowing of the lumen rather than hardening of the walls Calcification is inconstant and benign and does not interfere with blood flow Recent studies demonstrated no correlation between occlusions in an extremity and degree of calcification

Arteriography is of little value Interarterial injections of radiopaque mediums is uncomfortable and not without risk Clinical evaluation of the tissues in the periphery indicates whether adequate collateral circulation has been established Arteriography is valuable only in localizing an occluded area in the thigh preparatory to reconstructive surgery

Ancillary factors to be corrected most commonly are congestive failure *anemia diabetes and fresh arterial occlusions* In many patients correction of seemingly insignificant factors—such as night cramps abolished by quinine flatfoot corrected by arch supports the postphlebitic syndrome ameliorated by elastic bandages or gouty arthritis relieved by uricosurics—noticeably aids therapy

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(4) Ci [illegible] n 11 806-816 M y 1955

Treatment of Peripheral Vascular Disease with Cyclospasmol Review of 65 Cases is presented by R O Gillhespy[7] (Birmingham England) Cyclospasmol (trimethylcyclohexanol mandelate) a peripheral vasodilator can be given safely over a long period It has a spasmolytic nature similar to that of papaverine but is twice as effective and it reduces arterial spasm in addition to being a vasodilator

Of 29 men and 7 women with obliterative arterial disease and intermittent claudication given 100 mg cyclospasmol three times daily 19 had good 13 fair and 4 poor results Of 23 women and 6 men with Raynaud s disease given the same dosage 13 had good 8 fair and 8 poor results

Treatment of peripheral vascular disease remains a problem Since the fundamental cau e of senile obliterative arteritis is unknown and knowledge of Raynaud s disease has hardly increased since the original description there is little wonder that there is no specific treatment for either condition The patient can be offered only the possibility of symptomatic relief either by surgery or by medication Therapy that is successful in one case may be of no value in another apparently similar case Treatment should not be discarded as ineffective because it is not always helpful

To determine the full value of a drug of this type many more patients must be treated over long periods So far results with cyclospasmol are encouraging The drug is a valuable addition to the treatment of peripheral vascular disease

New Early Diagnostic Sign of Phlebitis of Lower Extremities is described by Teofilo Ortiz Ramirez and Ruperto Serna Ramirez[8] (Mexico City) Disease in the deep veins of the lower extremities remains difficult to diagnose A study was made of 32 patients with phlebitis 6 with varicose veins 12 with arteriosclerosis of the lower extremities 4 with thromboangiitis obliterans 2 with postphlebitic disturbances and 2 with nonspecific venous disturbances

METHOD —With the patient recumbent and the extremity slightly flexed a sphygmomanometer mercury cuff is applied above the knee and inflated to a pressure of about 4 cm Hg In patients with deep phlebitis pain wa induced in the lower extremity usually in the popliteal region or calf The pain increased for about five minutes sometimes equal to the spontaneou pain and disappeared almost in

(7) A g l gy 7 7 31 F b y 1956
(8) Am H t J 50 366 37 S pt mbe 1955

Aires) administered tromexan* (ethyl biscoumacetate) a derivative of dicumarol * to 21 patients with arteriosclerosis 5 with thromboangiitis obliterans (Buerger s disease) and 3 with Leriche s syndrome

For thrombosis to occur two of the three known etiologic conditions must exist alteration in blood composition endothelial lesion or slowing of the circulation with subsequent deposition of platelets In arteriosclerosis obliterans and Leriche s syndrome the endothelium is damaged and circulation is decreased In thromboangiitis obliterans the intima is thickened and altered

The starting dose of tromexan* was 600 1 200 mg and maintenance dosage was 75 or 150 mg every 12 hours modified by the prothrombin times The prothrombin time by the Quick test was maintained between 30 and 50% activity and was determined at eight day intervals Duration of therapy was 20-480 days If prothrombin fell to dangerous level vitamin C and rutin were administered

Of the patients with arteriosclerosis obliterans 18 had intermittent claudication Within 15 90 days 13 were subjectively improved Paresthesias disappeared in 12 of 16 patients nocturnal pains disappeared in 7 and were noticeably improved in 3 of 10 and ulcers were completely healed in 2 and improved in 3 patients Arterial pulsations were improved in 8 patients of 19 studied

All five patients with Buerger s disease had intermittent claudication During therapy the symptoms disappeared in three were improved in one and unchanged in one Paresthesias in four patients were improved in three Nocturnal pains disappeared in both patients previously afflicted Localized cyanosed spots and ecchymoses disappeared in three of four patients Ulceration in one patient remained unchanged Pulsations absent in all five patients returned in three

Paresthesias in two patients with Leriche s syndrome completely disappeared Nocturnal pain also disappeared Perionyxis with trophic skin alterations was present in one patient and cleared completely within 30 days Pulsations were absent in all three cases and were unaffected by therapy

Long term treatment with tromexan* was effective for arteriosclerosis obliterans Buerger s disease and Leriche syndrome

pear was the indurated and thrombosed vein which sometimes took one to two weeks to shrink to a fibrous cord

Superficial phlebitis was most common in varicose veins Of 104 patients in this category 102 were effectively treated by a single course of phenylbutazone Saphenous vein ligation and stripping were recommended after convalescence The two patients who did not respond were later found to have lymphosarcoma of the small bowel and carcinoma of the uterus respectively In seven other patients with malignant disease and superficial phlebitis five responded completely and in two the phlebitic activity was lessened Seven patients with superficial thrombophlebitis as part of active thromboangiitis obliterans responded readily to therapy Five patients had superficial phlebitis after the therapeutic introduction of irritants into regional veins and six patients had superficial phlebitis in apparently normal veins The involved veins were rapidly and successfully resolved with phenylbutazone

When phenylbutazone is given to patients who have deep vein thrombosis the pain and systemic reactions are definitely lessened However the most prominent feature swelling of the limb distal to the obstructed segment remains unchanged The swelling results from mechanical plugging of the main channels of venous return and is not due to the localized inflammatory edema of superficial phlebitis Phenylbutazone is advocated for the therapy of superficial phlebitis not for deep vein thrombosis

Inhibition of Experimental Venous Thrombosis Some Clinical Applications Irwin D Stein[1] (Mount Vernon N Y) injected glycerin or sodium tetradecyl sulfate into the marginal ear vein of rabbits Phenylbutazone was given to some rabbits intramuscularly before and after the irritant had been injected and to others after the vein had thrombosed

A firm fibrin and red cell clot was present three hours after the injection whether or not phenylbutazone had been given Differences first became apparent at six hours The animals who had received phenylbutazone had a healthy fibrin clot with few leukocytes and no escape into the stroma In the unprotected animals there were leukocytes in the periph

(1) A g logy 6 403-407 Oct ber 1955

stantly after pressure was released. The test result was not considered positive unless the pain appeared increased with pressure and disappeared immediately when pressure was released

The cuff sign was present in all patients with phlebitis Homan s sign was present in only 81% Bailey s sign in 44% Newman s sign in 25% Moses sign in 68% Castaneda Uribe s sign in 27% and swelling of the calf in only 36% None of the patients with varicose veins had a cuff sign 4 of the 12 patients with arteriosclerosis had some sign of phlebitis by other tests and only 2 had positive reactions to the cuff test Of the four with Buerger s disease two had a positive cuff test reaction

The venous hypertension induced by compression of the thigh results in distention of the subjacent venous system The painful effects are similar to those caused by mechanical external influences

Even though the cuff sign was present in 100% of the patients with phlebitis compared with 81% displaying Homan s sign it is not considered pathognomonic of phlebitis since the patient material was not homogeneous and the diagnosis of incipient phlebitis never can be sustained with absolute certainty

Further Observations on Treatment of Superficial Thrombophlebitis with Phenylbutazone (Butazolidin®) are made by *Irwin D Stein*[9] *(Mount Vernon N Y) who treated* 132 patients Many had been refractory to bed rest elevation of the extremity local applications of heat or cold anticoagulants and antibiotics

Each patient took 200 mg phenylbutazone three times daily for three days then 100 mg three times daily for four days a total of 3 Gm during the week Gastric irritation was prevented by taking the medication after meals Bed rest was not enforced unless the pain was incapacitating or the patient had a systemic reaction to the phlebitis Within 24 hours most patients were up and around

The earliest response was decreased pain apparent to the patient 8 12 hours after the first dose By the end of 24 hours local redness and swelling over the inflamed vein had regressed and the systemic fever had declined Thereafter improvement was progressive The last physical sign to disap

(9) C culat 1 833 837 N mbe 1955

Arbitrary time limits for subacute glomerulonephritis are 3 12 months Kidneys are normal sized or enlarged the capsule is slightly adherent and the surfaces are pale and smooth Microscopically changes of both acute and chronic glomerulonephritis are present and differentiation from chronic stages may be difficult Renal dysfunction is associated with marked proliferation of capsular cells and fibrous changes in glomeruli

Chronic glomerulonephritis occurs months or years after initial acute nephritis and is due to prolonged or recurrent diseases History of an acute attack may be absent Kidneys are small with surfaces coarsely granular cobbled and gray and the capsule is thickened The cortex is thinned and the corticomedullary markings indistinct Hyalinized glomeruli are common crescents may be present and the number of glomeruli and tubules is reduced the latter being atrophic or dilated and lined with flat epithelium Interstitial tissue is frequently fibrotic Renal insufficiency is due to extensive glomerular injury

Focal glomerulonephritis is most often associated with subacute bacterial endocarditis Grossly the kidneys may appear normal Micro copically hyaline thrombi are present in the glomerular capillaries with necrosis of these vessels Usually the glomeruli are not sufficiently involved to impair renal function

Membranous glomerulopathy is characterized by marked alterations of the glomerular tuft particularly the ba ement membrane usually without major evidence of cellular proliferation The e lesions may be classified as diabetic glomerulosclerosis lupus erythematosus membranous glomerulo is (lipid nephrosis) amyloidosis and eclampsia

Pyelonephritis may be acute chronic or healed and urinary outflow may be obstructed The infecting organism usually enters hematogenously or in urinary stasis by direct infection of the stagnant column of urine or through the periureteral lymphatics In the acute stage there are zones of extensive necrosis and absces es with edema and inflammatory infiltrate in the interstitial tissue The chronic stage characteristically shows broad deep cars and lymphocytic infiltration Involved tubules are dilated with epithelium flat and lumens filled with a hyaline colloid like coagulum

ery of the fibrin clot and escape into the perivascular stroma

By nine hours a huge clot was present in the control animals with massive infiltration of perivascular tissue with leukocytes The animals who had received phenylbutazone had only small spongy clots with a rim of leukocytes and slight stromal infiltration These differences were more marked at 12 24 and 48 hours In the animals treated with phenylbutazone no difference was detected between those started before or after the clot was induced

Phenylbutazone has been used clinically in the treatment of 132 patients with superficial thrombophlebitis 200 mg given three times daily for three days and 100 mg three times daily for the rest of the week Venous inflammation had previously been refractory to bed rest elevation of the limb moist applications anticoagulants antibiotics and interdiction of smoking Therapeutic effect was noted in 24 72 hours and after a week of treatment phlebitis as a rule did not recur No toxic reactions were seen except for a measles like rash in five patients

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THE KIDNEY

Basic Pathology of Common Renal Diseases is reviewed by John B Hazard and Lawrence J McCormack (Cleveland Clinic) The course of acute diffuse glomerulonephritis is generally less than three months Streptococcic infections are common precursors and autosensitization may be important Histology reveals endothelial and epithelial proliferation in the glomerulus with exudate hemorrhage into capsule spaces and tubules and changes in the glomerular basement membrane Depending on which of these features is prominent the disease is subdivided into proliferative exudative and hemorrhagic types Renal function is impaired when glomerular capillaries are blocked by proliferating endothelial cells glomerular basement membrane is altered capsular spaces obliterated by epithelial proliferation or tubules obstructed by blood The severe hematuria observed clinically is associated with minute ruptures of glomerular capillaries

( ) M Clin North Am 39 923 940 July 1955

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The healed phase is similar to the chronic but inflammatory response is milder Renal function is reduced by destruction of nephrons and in the acute phase by swelling of the kidney substance within the retaining capsule

Necrotizing renal papillitis is a severe form of pyelonephritis with a rapid course infection and destruction of pyramids by infarct necrosis *Micrococcus pyogenes* and *Escherichia coli* are common organisms The disease occurs with *diabetes mellitus* *Infarct necrosis due to thrombosis of capillaries* involve most or all pyramids Manifestations and death are due to infection or uremia

Acute diffuse interstitial nephritis is an uncommon usually fatal disorder associated with acute infectious diseases particularly diphtheria scarlet fever viral diseases and occasionally reaction to sulfonamides The enlarged kidneys resemble those in acute glomerulonephritis

Tuberculosis of the kidney usually is a hematogenous infection The organisms are excreted into the tubules form tuberculous foci in the medulla and caseous ulceration of the papillae The lesions are microscopically typical of tuberculosis

Vascular disease affecting the kidney is classified as arteriosclerotic arteriolar and malignant nephrosclerosis Renal involvement is part of a generalized process *affecting the* vessels Vascular changes are not limited to the kidneys In arteriosclerotic nephrosclerosis the renal artery and its larger branches are affected Occlusion causes localized death of renal tissue resulting in small wedge shaped cortical scars In arteriolar nephrosclerosis the small arterioles show fibrosis and hyaline thickening of the walls most marked in those near the glomerular tuft Focal loss of glomeruli and tubules may occur Hypertension *is* not always present Malignant nephrosclerosis is found in patients dying of rapidly progressive hypertension with associated uremia Microscopically vascular necrosis thrombonecrosis and onion peel lamination of the arterioles are noted

Acute tubular necrosis (acute renal failure) may be due to poisons principally heavy metals and organic solvents or intense *ischemia* as *in oligemic shock* The major site of chemical injury is the proximal convoluted tubule whereas in the ischemic form lesions have been reported throughout

the tubules Degree of anatomic change may be slight despite severe renal dysfunction Proximal tubular damage impairs selective absorption and distal damage permits abnormal absorption of waste products Casts obstruct some tubules Interstitial edema and swollen renal tissue further increase ischemia Polyuria is associated with early repair and the low functional status of healing epithelium

Polycystic renal disease is a common congenital familial malformation occurring equally in both sexes The cysts are most likely dilatations or herniations of functioning nephrons and collecting tubules that progressively enlarge The basic defect may be abnormal formation of basement membranes surrounding individual tubules Death usually is due to uremia At autopsy involvement is bilateral and grossly the kidneys appear completely replaced by cysts Small zones of functioning renal parenchyma can be seen microscopically About 15% of patients with polycystic kidneys have berry type intracranial aneurysms and about 4% of patients with these aneurysms have polycystic kidneys

• [This paper presents a concise summary of the pathology of most of the common renal di orders —Ed]

Concept of Renal Tubular Insufficiency with Descript on of Three Typical Cases is reviewed by Howard G Worthen and Robert A Good[3] (Univ of Minnesota) The renal tubule excretes nitrogenous wastes reabsorbs important nutritional components from the ultrafiltrate of plasma and regulates the acid base composition and osmotic pressure of body fluids Tubular damage accompanies most types of nephritis but in generalized kidney disease is overshadowed by glomerular malfunction Only small amounts of glomerular filtrate reach the tubules and sufficient function remains to prevent expression of underlying tubular disease Tubular insufficiency is the term applied to kidney disease in which tubular malfunction is the predominant feature

Hereditary renal glycosuria is a benign condition in which the renal tubules cannot reabsorb normal amounts of glucose The renal threshold for glucose is low Glucosuria is in ig nificant and the condition is a laboratory disease without clinical expression If the patient is restricted in carbohydrate intake ketosis may develop due to hypoglycemia

(3) Journ l La t 75 473-479 N mber 1955

Hereditary cystinuria—also benign—resulting in urinary loss of cystine lysine arginine and ornithine is a form of renal aminoaciduria that remains asymptomatic unless cystine calculi form in the urinary tract Wilson s disease and galactosemia are associated with aminoaciduria Secondary aminoaciduria may be due to vitamin deficiency or to tubular injury

Polyuria of nephrogenic diabetes insipidus is clinically similar to that of pituitary or hypothalamic origin but is unaffected by pitressin * The urine volume is determined by the amount of solute excreted when the solute load is high urine volume is high The defect seems to be deficient water retention by the convoluted tubules The only therapy is dietary restriction that decreases the obligatory solute load to the kidneys

By producing hydrogen and ammonium ions the kidney maintains the normal acid base balance in body fluids Excreting these ions permits reabsorption of equivalent cations (sodium calcium potassium) and excretion of more filtered anions than filtered cations resulting in acid urine and conservation of fixed base When these mechanisms fail fixed base may be lost and systemic acidosis may occur Hyperchloremic metabolic acidosis has experimentally been induced in man and animals by diamox * Potassium secretion apparently competes with hydrogen ion secretion If the latter is deficient the former is accelerated and hypopotassemia may result unless potassium intake is increased

Fanconi s syndrome is the prime example of renal tubular disease with failure to reabsorb normal amounts of glucose amino acid phosphorus or bicarbonate and apparently with ecretory inadequacies The proximal tubule is short and joined to the glomerulus by an abnormally narrow neck which may account for all the defects in renal function Maleic acid or maleate given to rats caused renal glycosuria aminoaciduria and phosphaturia an experimental model of Fanconi s syndrome which was not corrected by even massive doses of vitamin D In man such therapy reportedly benefited one patient did not another and results were equivocal in a third

Medical management of clinical disease caused by tubular disturbances is still not completely satisfactory Further basic research is needed

Treatment of Acute Renal Shutdown is discussed by Maurice B Strauss and Lawrence G Kaisz[4] (Boston) Urinary obstruction and dehydration must be ruled out in all cases of anuria or oliguria Irreversible causes of acute renal shutdown are bilateral renal infarction and acute cortical necrosis reversible causes are acute glomerulonephritis hemorrhagic papillary necrosis and acute tubular necrosis In treating a patient with acute renal shutdown any deficits of water red blood cells plasma and electrolytes must first be restored A patient who has lost gastrointestinal tract fluids requires isotonic sodium chloride or a sodium chloride sodium lactate replacement solution the latter if small intestine biliary or pancreatic juice has been lost The aim of further treatment is to maintain a reasonably constant extracellular fluid volume and to diminish the rate of accumulation of catabolic products by limiting protein breakdown until renal function returns In protein breakdown serum bicarbonate concentration and pH tend to fall serum calcium also falls while serum phosphorus rises Serum urea and potassium rise

Overhydration mu t be prevented during anuria and oliguria Daily weight is a good guide The daily fluid intake should equal the insensible loss of water from the skin and lungs which equals about 1 000 cc plus the pre formed water and water of oxidation which equal about 400 cc plus the urine output Endogenous protein catabolism is about 1 Gm /kg body weight/day and is increased by activity fever infections tis ue necrosis and metabolic response to injury Administration of 100 Gm dextrose daily will reduce endogenous protein catabolism by almost half and prevent ketosis Administration of exogenous fat is not necessary Theoretically a patient with acute renal shutdown should receive daily about 500 cc of 20% dextrose in water divided into two portion However with concentrations of 20% or higher the problem of venous thrombosis arises The 100 Gm dextrose daily is best given in a 15% solution even though the fluid intake must be slightly increased All fluids lost through emesis diarrhea sweating or extraneous drainage should be replaced by the appropriate solution Fluid lost through emesis is replaced by isotonic saline wound drainage loss by a mixture of 2 parts isotonic saline to 1 part

(4) A M A \ h I t M d 95 846 856 J 1955

isotonic sodium lactate and sweat loss by half strength isotonic saline Tetany should be corrected by calcium intravenously Hyperkalemia can be temporarily corrected by adding 1 unit of regular insulin to each 2 Gm dextrose

After the stage of oliguria stops and the patient begins to have diuresis salt and potassium losses must be prevented Fluid and electrolyte balance must be maintained until the urine volume reaches 3 or 4 L daily Potassium citrate should be given by mouth in doses of 3 5 Gm three to four times daily if the serum potassium falls below 3 5 mEq /L

Artificial methods of maintaining homeostasis during acute renal failure must be used when physiologic methods fail Cation exchange resins in the ammonium hydrogen or sodium phase are administered orally or rectally to exchange for potassium and can reduce serum concentrations from over 8 mEq /L to normal in one to three days Exchange transfusions have been used but are not advocated because of complications Intestinal lavage can remove substantial amounts of urea electrolytes and fluid from the body without special apparatus or surgery but removal is not precise and controllable Vomiting and abdominal distention may develop during prolonged lavage The procedure may be useful and benign early in acute renal failure when the patient has been given too much fluid It can be used when external dialysis and peritoneal lavage are contraindicated Peritoneal lavage can be used to remove retention products and correct body fluid abnormalities without undue risk It is contraindicated when there is an abdominal wound or infection

External dialysis with the Kolff artificial kidney is an excellent means of correcting the abnormal electrolytes in acute renal shutdown but it has certain disadvantages Bank blood is necessary the apparatus is complex heparinization of the patient is required and there is danger of hypertension

Mortality from acute tubular necrosis can be reduced to nearly zero by the combination of physiologic measures and external dialysis If an efficient dialyzer is available its use is safer and more comfortable than peritoneal lavage except when heparinization is contraindicated by bleeding

• [Cation exchange resins are especially valuable in patients who have elevation of blood potassium which is the common cause of death when

there is renal shutdown One must be certain that the resin used is potassium free—Ed]

Treatment of Nephrotic Syndrome in Children is reported in 40 patients by P Durand and E De Toni Jr[5] (Univ of Genoa) Various patients were treated with ACTH malaria thiosemicarbazone synthetic resins and nitrogen mustards Several received more than one type of therapy Of five receiving nitrogen mustard intravenously three showed increased diuresis and weight loss but edema gradually reappeared Proteinuria was moderately decreased but proteinemia cholesterolemia and serum electrolyte values were unchanged Improvement with this therapy was insignificant

Of five receiving a mixture of carboxylic potassium cation exchange and polyaminoformaldehyde type anion exchange resins two showed improvement (with increased diuresis reduced edema weight loss no proteinuria and normal cholesterolemia) which was only temporary This treatment was only partially successful

Of four receiving thiosemicarbazone only one showed marked increase in diuresis eight days after therapy was started Remission lasted five months The others had only partial responses

Malaria therapy is useful in treatment of the syndrome and is best induced by intramuscular inoculation of malarial blood Among 10 patients edema completely disappeared and blood chemistries became normal in 6 blood cholesterol levels were reduced total protein and albumin levels increased and proteinuria was reduced or abolished

Of 16 treated with ACTH 6 who received large doses (100 200 mg daily) had complete remission In five treated with moderate doses (40 50 mg daily) and five with large doses remission was temporary At the beginning of therapy diuresis was reduced and edema increased Between the sixth and eighth days or when ACTH was discontinued diuresis increased proteinuria was sharply reduced or completely disappeared serum protein and albumin levels increased and cholesterol levels reached normal or subnormal If doses are high enough and cycles are repeated at short intervals ACTH is the most practicable and efficient treat

(5) A p ed t 185 2 5 35 O tobe 1955

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• [Cation exchange resins are especially valuable in patients who have elevation of blood potassium which is the common cause of death when

compensation Antidiuretic hormone and adrenal corticosteroids are antagonistic in their effect on water balance

Criteria have not been established for selection of patients to have this therapy All patients refractory to the usual therapeutic measures were considered eligible but further experience based on trial error and experiment are necessary

Edema Caused by Retention of Sodium Chloride with Hyperaldosteronuria Attempt at Classification of States of Hyperaldosteronism. R S Mach J Fabre A F Muller and R Neher[7] review clinical and experimental studies relating to aldosterone metabolism and report a case

Woman 46 for more than 20 years had had generalized edema with headaches visual disturbances transitory aphonia and arterial hypertension Swellings which involved the legs hands arms and face disappeared whenever she followed a salt free diet or received diuretics and reappeared every time she took over 4 Gm salt particularly during tests when an excess of salt was administered No evidence of renal cardiovascular or hepatic lesions was noted She had no thyroid deficiency no signs of Cushing s corticoadrenal syndrome and no obesity In three separate tests increase of urinary aldosterone was demonstrated

The normal weight excluded the obesity of salt and water described by Zondek The case resembled that described by Jungmann in 1922 as isolated sodium chloride metabolic disturbance Similar cases have been reported since then among other that described by Laude as oliguria from sodium chloride retention but pathogenesis has remained obscure Discovery of increase of urinary aldosterone on three occasions in the authors patient suggests a new interpretation of this type of edema A relation is postulated between retention of water and salt and hyperaldosteronuria Increase of aldosterone in the organism with its effects on metabolism of electrolytes and water seems enough to account for the complete syndrome

With present extraction methods it was estimated that 1 5-6 µg aldosterone is normally excreted in urine in 24 hours In the authors patient this was increased to 18 µg The value falls to zero in patients with Addison s disease and in adrenalectomized animals conversely a normal amount of aldosterone is maintained in patients with panhypopituitarism or hypophysectomized persons These findings con

(7) Schw med W h sch 85 12 9 1234 Dec 17 1955

ment Despite progress no treatment is really specific Various therapies give good results in most cases but no method is successful in all cases

Clinical Use of Corticotropin (ACTH) and Adrenal Corticosteroids in Therapy of Intractable Edema G H Heidorn and F R Schemm[6] (Great Falls Mont) treated 10 patients with nephrotic syndrome 21 with refractory cardiac edema and 2 cardiac patients with sodium dilution syndrome The 21 cardiac patients included 8 with arteriosclerotic cardiovascular disease 8 with rheumatic heart disease 3 with hypertensive heart disease and 2 with chronic cor pulmonale The dose of ACTH varied from 5 to 25 mg every six hours intramuscularly

Diuresis induced by ACTH in patients with the nephrotic syndrome began abruptly and spontaneously after the therapy was stopped usually within 24 hours likewise in patients with edema of cardiac origin The diuresis was most often water in excess of sodium although proportionate losses and even loss of sodium in excess of water occurred Edema loss occurred during ACTH therapy in both renal and cardiac patients The diuresis and negative sodium balance usually began about the fifth or sixth day of hormone therapy

By some unknown mechanism ACTH caused patients who before therapy were refractory to mercurial diuretics to regain sensitivity

Successful diuresis was induced in 6 of the 10 patients with the nephrotic syndrome 18 of the 21 with cardiac disease and intractable edema and in both patients with cardiac disease and sodium dilution

Edema formation in cardiac decompensation and nephrosis is apparently due at least in part to a disturbed balance between antidiuretic and diuretic factors An increased antidiuretic effect can be produced by increased concentrations of the antidiuretic principle from the posterior pituitary or by decreased production of adrenal corticosteroids in an exhausted adrenal cortex resulting in an unopposed antidiuretic effect of the antidiuretic hormone Both situations have been noted in patients with long standing cardiac de

(6) Am J M Sc 2 9 6 1 631 J 1955

to tissues where significant toxicity apparently does not occur Continued administration increases tolerance and a dose which would have been fatal becomes innocuous if preceded by several days of sublethal loading

In about half the patients with severe azotemia serum potassium levels spontaneously reach over 5 5 mEq /L Levels above 6 5 or 7 mEq are uncommon and occur only with severe oliguria although oliguria is not always associated with marked hyperpotassemia Spontaneous hyperkalemia sufficient to cause death occurs only with general deterioration of renal function in the terminal phase of chronic renal insufficiency Despite great reductions in functioning renal mass the damaged kidney may still excrete normal amounts of potassium Serum concentrations of 8 mEq /L have been noted without serious clinical consequences

Conservation of potassium by the kidney is relatively inefficient Restriction of sodium and potassium apparently augments efficiency of renal conservation of potassium Urinary potassium excretion may be useful clinically as an index of potassium depletion because less than 10 mEq /24 hours indicates chronic potassium depletion even though serum levels are not greatly lowered Low urinary potassium excretion also virtually excludes impaired renal conservation as the cause of potassium loss No case of demonstrated renal potassium wasting has ever been reported in a severely azotemic patient Adrenal tumors have been responsible for some cases of unexplained renal potassium wasting but one patient has been reported who had only malignant nephrosclerosis without adrenal abnormality During the diuretic phase of acute renal insufficiency when damaged tubules cannot conserve electrolytes and water potassium and other cations may be lost in significant amounts

Adrenal hormones and desoxycorticosterone accelerate potassium excretion which probably depends on increased sodium reabsorption with exchange of potassium for the sodium ions Restricted sodium intake minimizes loss of potassium Potassium diuresis occurs in subjects on a low sodium diet or adrenal steroids if they are given sodium paraminohippurate or sodium sulfate in patients with cirrhosis or severe congestive heart failure given ammonium chloride

firm the well known clinical observation that the mineral function of the cortex has a certain autonomy, independent of the hypophysis since in anterior pituitary deficiency the dehydration characteristic of Addison s disease is never observed Injection of ACTH in man does not influence e cretion of aldosterone to the same extent as do other steroids

Increased excretion of aldosterone can be observed under the following conditions (1) Physiologic variations related to homeostatic regulation of electrolyte and water balance which may be stimulated by restriction or loss of NaCl ex cess of K or reduction of fluid volume (2) Pathologic hyper production of aldosterone leading to the syndrome of deple tion of potassium with hypernatremia and polyuria caused by a tumor of the adrenal cortex (Conn s primary aldosteron ism) or the syndrome of sodium retention with edema de scribed in the present case (3) Chronic secondary hyper aldosteronism due to nephrotic cardiac or cirrhotic edema or to various states involving retention of NaCl e g toxemias of pregnancy and hypertension Hyperaldosteronism accom panying these edematous states is not well understood but may be related to diminution of circulating fluids

• [Not all patients with excessive formation of aldosterone display a significant amount of edema Hypertension may be the outstanding f a ture The combination of hypertension and/or edema associated with per sistent elevation of sodium and depression of potassium of the plasma should lead to the suspicion of hyperaldosteronism Tumors of the adrenal cannot be demonstrated in every instance —Ed]

Potassium and the Kidney are reviewed by William B Schwartz[8] (Tufts College) The potassium content of cells probably regulates potassium excretion and conservation as wide fluctuations in potassium excretion occur independent ly of plasma concentration or filtered load Potassium must be secreted by the renal tubules by an ion exchange for sodi um in the glomerular filtrate

Rapid oral administration of potassium up to 1 mEq /kg body weight produces little change but large doses 2 5 mEq /kg sharply elevate serum potassium levels sugge t ing that even with normal kidney function large amounts of potassium may be hazardous though as much as 640 mEq has been ingested daily without ill effect Most of the re tained potassium is transferred from the extracellular space

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potassium replenishment separate renal abnormalities due to primary renal disease from secondary functional disturbances due to potassium deficiency Biopsy revealed that the primary renal disease was chronic pyelonephritis which led to reduced glomerular filtration rate and tubular acidosis Potassium deficiency seemed responsible for reversible renal phosphaturia impaired sodium conservation and possibly reduced osmolar concentrating capacity It affected the metabolism of nitrogen and phosphorus

Potassium is essential for protein synthesis in man and affects capacity for phosphate absorption by the renal tubules and possibly by the bowel No abnormality of excitability or disturbance of lactic acid formation could be demonstrated in the weak potassium-depleted voluntary muscles in the patient

In a patient sustaining large renal losses of potassium possibility of adrenocortical overactivity must be excluded Radical removal of a secreting adrenal tumor in primary aldosteronism and adrenal surgery for Cushing s syndrome may induce complete cure When potassium wastage is due to renal disease potassium must be supplemented

Early diagnosis of renal potassium loss is difficult Even minimal proteinuria history of previous renal disease and especially nocturia should suggest that homeostatic renal insufficiency may underlie vague weakness and ill health

Chronic Hypopotassemia of Renal Origin E G Sayer K I D Eyre and F H Sims[1] (Auckland New Zealand) report on a woman aged 37 with chronic hypopotassemia muscular paralysis and mild renal disease The syndrome was similar to primary aldosteronism but alkalosis was absent and signs and symptoms were completely relieved by potassium chloride orally Excessive potassium loss in chronic nephritis and resultant low serum potassium levels are not uncommon but depletion severe enough to cause muscular weakness and paralysis is comparatively rare

Renal damage was very slight Glomerular filtration rate was normal and effective renal plasma flow was only slightly diminished Reabsorptive capacity of the proximal tubules was diminished Distal tubular function measured by potassium response to a carbonic anhydrase inhibitor was normal

(1) Lancet 2 63 68 July 9 1955

mercurial diuretics or a carbonic anhydrase inhibitor and in nephrotic patients infused with sodium paraminohippurate Prior potassium depletion curtails potassium diuresis which would ordinarily occur from hyperventilation alkali loading or administration of a carbonic anhydrase inhibitor

Potassium and hydrogen share and compete for a common secretory mechanism When potassium is in excess in the tubular cells hydrogen secretion is diminished and the urine becomes alkaline When the tubules are depleted of potassium hydrogen secretion increases and the urine becomes acid Transfer of hydrogen ions from extracellular fluid to the tissues in exchange for intracellular potassium initially elevates the plasma bicarbonate concentration but the kidney is ultimately responsible for correction of alkalosis

Renal dysfunction may be caused by chronic potassium depletion and function improves when the deficit is restored Renal biopsy in two patients revealed hydropic degenerative changes in the proximal tubular epithelium In patients with renal disease potassium depletion due to vomiting or diarrhea may further impair renal dysfunction The azotemia commonly seen after surgery may be due to sodium depletion dehydration and shock and possibly to potassium depletion Changes in renal function previously ascribed to alkalosis may be partly due to potassium depletion It is also probable that potassium depletion causes renal dysfunction in patients with adrenal tumors who produce excess aldosterone

Potassium Losing Renal Disease Renal and Metabolic Observations on Patient Sustaining Renal Wastage of Potassium are reported by R F Mahler and S W Stanbury[9] (Manchester Royal Infirm)

Woman 63 due to combination of anorexia and failure of renal conservation of potassium became depleted of about half the total body potassium Symptoms included muscular paralysis thirst dehydration and nocturia Serum potassium and phosphate levels were low Despite inability to produce maximally acid urine she showed no metabolic acidosis Biochemical abnormalities were corrected and all symptoms except nocturia relieved by potassium bicarbonate and a low sodium diet Paralytic ileus which developed after cholecystectomy was related to inadvertent recurrence of potassium deficiency

Detailed metabolic and renal studies before and during

(9) Q rt J M d 25 1 52 J n y 1956

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(1) La et 2 63 68 J ly 9 1955

No acidosis alkalosis, failure of hydrogen ion production or abnormal base conservation was noted

No history of urinary tract infections was obtained and cultures of two catheterized specimens produced no organisms The only suggestive finding was a slightly abnormal pyelogram History of persistent mild hypertension aggravated during pregnancy suggested mild nephrosclerosis Renal damage remained unchanged during two years observation

Supplementary potassium abolished the symptoms of generalized weakness and the sudden attacks of paralysis The ECG reverted to normal and urea clearance was definitely improved

The renal lesion probably was mild impairment of tubular function Diminished proximal tubular reabsorption of potassium was responsible for the unusually large urinary losses

Intercapillary Glomerulosclerosis Pathogenic and Clinical Features and Treatment, Based on Study of 100 Cases are reported by Arthur M Clark and Penn G Skillern (Cleveland Clinic) The cause is unknown Unknown biochemical changes part of the metabolic abnormality in diabetes have been implicated Pathognomonic combined features are hypertension (present in 88 of the 100 patients) diabetic retinopathy (96 of 99 patients) albuminuria (98 of 100 patients) hypoalbuminemia with or without edema (69 of 73 patients) uremia (66 of 100 patients) and anemia (77 of 96 patients)

In young patients with diabetes incidence of intercapillary glomerulosclerosis is about equal in both sexes but in older patients the condition is more common in women because incidence of diabetes is higher in women Incidence is higher in patients over 50 reflecting the higher incidence of diabetes mellitus in the older age group and the fact that diabetes usually must be present for several years before this renal complication occurs The two most important known clinical pathogenic factors are duration and degree of control of diabetes

Diagnosis is fairly accurate in presence of characteristic clinical features of hypertension edema retinopathy renal

(2) M Clin North America 39 1001 1013 July 1955

failure albuminuria and hypoalbuminemia Definite diagnosis depends on renal biopsy or autopsy Among the 100 patients clinical diagnosis was confirmed pathologically in 10

Presence and severity of resulting hypertension usually is directly proportional to severity of the disease process in the kidneys Though an important diagnostic criterion hypertension may be absent in some patients Diabetic retinopathy usually antedates clinical symptoms and severe grades of retinopathy are more likely to be associated with the renal lesions although several patients with severe retinopathy had no evidence of intercapillary glomerulosclerosis and three patients with intercapillary glomerulosclerosis had no retinopathy

Intercapillary glomerulosclerosis is a complex disorder often resistant to treatment Diabetes must be controlled A high protein diet may be helpful if hypoalbuminemia is present and edema may respond to a low salt diet and mercurials Mild antihypertensive drugs may be indicated

Effect of Reserpine and Its Combination with Hydralazine on Blood Pressure and Renal Hemodynamics during Hypertensive Phase of Acute Nephritis in Children James N Etteldorf J D Smith and Curtis Johnson[3] (Memphis Tenn) treated 20 children aged 3 10 years with intramuscular injections of reserpine 0 07 mg /kg and hydralazine 0 15 mg /kg All had acute nephritis with hypertension hematuria albuminuria oliguria and periorbital edema

Reserpine alone effectively reduced the blood pressure in about 40% of the patients When given before or simultaneously with hydralazine reserpine enhanced and prolonged the response of hydralazine for 12 hours or longer after reserpine was given

The combination of reserpine and hydralazine uniformly reduced the elevated blood pressure in children with nephritis The simultaneous administration is especially recommended in the presence of encephalopathy or cardiac failure This combination given once is adequate for most patients No undesirable side effects were noted and renal function was minimally affected The drugs probably are the best available therapeutic agents for control of hypertension in nephritis

(3) J P diat 48 1 9 139 F bru ry 1956

Cardiovascular and Renal Responses to Combination of Hexamethonium and 1 Hydrazinophthalazine (Apresoline*) in Hypertensive Subjects David H Stein and Hans H Hecht[4] (Univ of Utah) studied 18 patients 15 with essential hypertension and 3 with renal disease and hypertension

Eight patients received apresoline* intravenously Of four with normal resting renal plasma flow and glomerular filtration rates three had appreciable increase and one decrease in renal plasma flow In four with below normal resting renal plasma flow and glomerular filtration rates no change was elicited by apresoline*

Of seven hypertensive patients five had obvious increase in cardiac output after the drug was injected Moderate decrease in arterial pressure and rise in pulse rate were noted in all seven In the two patients in whom cardiac output did not rise hypotension and shock developed

Hexamethonium intravenously produced autonomic blockade moderate reduction of supine blood pressure and little or no reflex rise in pulse rate Rise in pulse rate did not occur if hexamethonium was administered and then followed by 1 hydrazinophthalazine

In nine patients renal plasma flow and glomerular filtration rate fell slightly simultaneously with fall in blood pressure after hexamethonium When 1 hydrazinophthalazine was injected only the three patients with normal resting renal flow had a significant rise

All patients given both drugs had decreased arterial pressure and little change in pulse rate The expected rise in cardiac output was blocked by hexamethonium Patients who could increase the renal plasma flow did so after 1 hydrazinophthalazine therapy and this effect was not blocked by hexamethonium

Combined use of both drugs in treating hypertension may be rational The hypotensive effects are greater and increase in renal plasma flow when possible still occurs but increase in cardiac output and cardiac work is partially or completely blocked

• [In patients with coronary disease apresoline* may increase cardiac work by causing increased output and precipitate anginal attacks The

(4) J Cl 1 e t 34 867 874 J 1955

study of Stein and Hecht would indicate that this risk is diminished if hexamethonium is used also Likewise the study would indicate that the effect of the latter drug in decreasing renal plasma flow tends to be overcome by simultaneous administration of 1 hydrazinophthalazine The study supports the idea that the two drugs together are probably more valuable and safer in the treatment of hypertension than either alone —Ed 1

Pentapyrrolidinium and Kidney Function V Rønnov Jessen studied the effects of pentapyrrolidinium (ansolysen®) on the glomerular filtration rate renal blood flow and excretion of salt and water during short and long term therapy Intravenous injection of the drug produced simultaneously a fall in blood pressure considerable reduction of the urine flow and some decrease of inulin and para aminohippurate clearances In one patient inulin clearance increased despite lowered mean blood pressure The filtration fraction increased in four patients decreased in two and was unchanged in three The decrease in urine output was accompanied by reduced sodium and chloride excretion while that of potassium was not changed Given for several days the drug reduced the excretion of water and sodium chloride

Five patients were examined before and after the use of the drug orally for 40 75 days In four the glomerular filtration rate increased 10-67% and the renal plasma flow 9 78% In one patient both parameters remained unchanged

Ansolysen® intravenously has almost the same effect on kidney function as hexamethonium In a few patients the drug may lead to heart failure because of its water and salt retaining effect

Diagnosis and Treatment of Pyelonephritis is reviewed by Robert D Taylor[6] (Cleveland Clinic) Pyelonephritis an infectious process the commonest of all kidney diseases can lead to renal failure and death In many patients who died of pyelonephritis diagnosis was not made ante mortem

Pyelonephritis is usually caused by the colon bacillus but sometimes by Streptococcus faecalis Pseudomonas aeruginosa Aerobacter aerogenes or Bacillus proteus Kidney parenchyma is invaded by localized inflammatory lesions which are repaired and replaced by scar tissue Tubules and glomeruli are involved in this process which if uncontrolled results in contracted kidneys

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Some patients do not have costovertebral angle pain chills fever dysuria pyuria proteinuria or bacilluria and diagnosis is made only after renal insufficiency or cryptogenic anemia is found All patients suspected of having pyelonephritis should have x rays of the urinary tract if renal function permits an intravenous pyelogram is best Instrumentation should be avoided but if cystoscopy and retrograde pyelography are necessary they should be done only after the infection is maximally controlled and the blood urea value no more than 100 mg /100 ml

Urine cultures and sensitivities are helpful but the patient should not be catheterized After the glans penis or urethral meatus is cleansed with green soap and painted with zephiran® chloride solution the patient should void a small amount into a sterile container discontinue the stream and pass the rest into a sterile vessel from which the culture is made

Addis counts are the most valuable diagnostic aid Specific gravity after 24 hour s fluid deprivation is less than 1 026 in patients with pyelonephritis Proteinuria ranges from less than 0 2 to 3 Gm /24 hours pyuria exceeds the normal of 1 000 000 cells/24 hours and hematuria is more than 500 000 In active infection cylindruria is more than the normal (3 000/12 hours)

Treatment should be continued for several weeks after all signs have been controlled Fluids should be 2 500 3 000 cc daily and may include coffee tea and alcohol Oxytetracycline or tetracycline is given (250 mg four times daily) for five to seven days and 0 5 Gm sulfadiazine four times daily for six weeks The condition is then re evaluated Recurrent attacks may require 0 5 Gm sulfadiazine four times daily or 100 mg oxytetracycline four times daily for two weeks of each month

Treatment of Tuberculous Infections of Genitourinary Tract was reviewed by John K Lattimer[7] (Columbia Univ) Chemotherapy with a combination of drugs should be continued uninterruptedly for a year Best results were obtained with 1 Gm streptomycin twice a week 100 mg isoniazid three times daily and 5 Gm sodium para aminosalicylic acid three times daily Surgery for renal tuberculosis was supple

(7) J U ol 74 91 300 Sept mber 1955

mented with a year of chemotherapy During seven years 625 patients were treated

Tuberculosis of the genitourinary tract occurs in about 4% of all patients with pulmonary tuberculosis Occasionally the kidney is destroyed over 10 years rarely in 3 years Renal tuberculosis may lie dormant for many years with onset of symptoms between age 25 and 30 and in some after age 45

Half the patients had initial complaint of epididymitis always secondary to renal tuberculosis which in turn was secondary to pulmonary lesions Every patient with pulmonary tuberculosis should be carefully followed for 10 years for renal symptoms When symptoms occur 24 hour urine samples should be studied by culture and guinea pig inoculation A woman with a tuberculous lymph node in the groin was infected from the tuberculosis in the scrotum of the husband who had renal tuberculosis

Five year mortality in patients with bilateral renal tuberculosis who received combined therapy was only 8% Before chemotherapy the average mortality was 80% Advanced unilateral renal tuberculosis is probably best treated by nephrectomy with chemotherapy for four months before and eight months after nephrectomy Refractory tuberculous lesions confined to one portion of the kidney can be resected

Contracted bladder occurred in about 10% of the patients Prostatic tuberculosis also responded to chemotherapy although nodules did not disappear Small hard nodules on the epididymis were common and shrank very slowly after chemotherapy

Clinical Value of Renal Biopsy is reported by Robert M Kark Robert C Muehrcke Conrad L Pirani and Victor E Pollack[8] (Chicago) Almost 800 biopsies have been done by four groups of investigators without mortality and with little morbidity Contraindications are progressive severe uremia hemorrhagic diathesis lack of co operation severe calcific atherosclerosis and hydronephrosis

Difficulties in finding the organ with the biopsy needle may be obviated by using intravenous pyelograms and an atraumatic fine exploring needle to locate the lower pole of the kidney before the Franklin Vim Silverman biopsy needle is inserted With the patient prone a sandbag under the ab

(8) A I t M d 43 807 847 O t be 1955

domen pushes the kidney toward the back and insures hemostasis after the biopsy has been taken When the portion of needle outside the skin swings in a wide arc with deep inspiration the point of the exploring needle is in the kidney Diagnosis is more accurate by kidney biopsy than by any other method At present occult infection of the kidney can be diagnosed only by biopsy Among the first 200 biopsies cultures of tissue were positive in five instances in which the urine was repeatedly negative on culture In each instance the organism was eradicated by appropriate antibiotic therapy and abnormal urine findings were restored to normal Biopsies have also been valuable in prognosis especially in the nephrotic syndrome hypertension pyelonephritis lupus erythematosus disseminatus toxemia of pregnancy and diabetes

Of 32 patients with lupus erythematosus disseminatus 5 had the nephrotic syndrome and 3 had all the clinical features of the nephrotic syndrome except that serum cholesterol level was low The renal lesion of lupus nephritis may be local glomerulitis which progresses to subacute glomerulonephritis with crescent formation or it may begin as a thickening of basement membrane with wire loop lesions and may pass into membranous glomerulonephritis Patients with local or generalized glomerulitis have white cells in the urine and mistaken diagnosis of pyelonephritis may be made

In a number of patients with protein free urine biopsy sections showed proteinaceous material in Bowman s space and the tubular lumens confirming the concept that protein is filtered by the glomeruli and reabsorbed by the tubules

Complications from renal biopsy were relatively minor Among 200 attempts at biopsy no deaths occurred and surgical intervention was never necessary Retroperitoneal hemorrhage did not occur and no infection was disseminated from an infected organ The procedure was painless except for five patients with transient renal colic due to small clots of blood in the ureter Seven patients had transient back pain two had intermittent hematuria and one with calcific atherosclerosis bled into the bladder but recovered uneventfully

Puerperal Vasomotor Collapse in Patients with Toxemia of Pregnancy—New Concept of Etiology and Rational Plan of Treatment This serious complication of toxemia usually

leads to death Howard J Tatum and James G Mule[9] (New Orleans) determined the serum electrolyte levels in patients during vasomotor collapse and found abnormally low concentrations of sodium and chloride with hyperpotassemia Sixteen patients were given sodium chloride 0 9 or 3% intravenously an average of 10 3 Gm in 800 cc water Within an hour vessel tone was restored blood pressure returned toward precollap e level and serum sodium concentrations increased toward normal The clinical change was dramatic and none of the 16 patients died

This type of vasomotor collapse may be analogou to that of acute adrenal insufficiency In both conditions serum sodium and chloride levels are low and serum potassium level high In toxemia of pregnancy sodium retaining corticoids are increased shifting sodium out of the vascular system into the extravascular compartments Urinary excretion of sodium is decreased and sodium balance is positive In Addison s disease sodium retaining corticoids are deficient permitting excessive sodium lo s by the kidney The placenta actively produces adrenal like hormones with consequent atrophy of the adrenal glands in patients with eclampsia Therefore in some patients with toxemia relative adrenal cortical insufficiency may develop shortly after delivery

Vasomotor collapse in these patients probably is due to restricted salt intake the shift of sodium to extravascular compartments and some degree of adrenal cortical insufficiency Although a series of 16 patients is too small for statistical analysis survival of all contrasts sharply with usual high mortality Sodium chloride is suggested as specific therapy for vasomotor collap e that develops after delivery in patients with toxemia of pregnancy

(9) Am J Obst & Gy ec 71 492 501 M h 1956

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The Digestive System

FRANZ J INGELFINGER M D

PART V

THE DIGESTIVE SYSTEM

ESOPHAGUS

Dysphagia Lusoria Study of 15 Cases of Aberrant Right Subclavian Artery J Horacio Resano and Julio Cesar Barani[1] believe that although physicians generally know what dysphagia lusoria is only a few are able to diagnose it from its radiologic picture Once the picture is fixed in the mind diagnosis is easy The term dysphagia lusoria was first used in 1794 by Bayford but was later extended to include all disturbances of deglutition caused by anomalies in the origin and course of the great arteries related to the esophagus The term should however be restricted to the dysphagia caused by an aberrant right subclavian artery Such an aberrant artery travels obliquely upward to the right and across the midline passing between the esophagus and the spine in most cases in only 10% of one series of 193 cases did it pass between the esophagus and the trachea and in only 3% was it in front of the trachea Although the condition is usually considered rare the authors identified it in 15 cases during the years 1953 and 1954

The dysphagia in this condition which sometimes appears first in adulthood and sometimes reappears years after infancy may consist of only a slight retention of food eaten hastily Regurgitation is rare and occurs only when large solid mouthfuls are insufficiently masticated Figure 78 explains the characteristic radiologic signs seen on esophagography chief of which is the pathognomonic notching of the esophagus A front view shows the notch in the left edge of the esophagus at the level of the aortic arch The supra aortic segment of the esophagus is typically displaced above the aortic arch from compression by the aberrant right subclavian artery which pushes it away from the arch A left

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(1) R f J m l pa m 2 395-411 A t 1955

PART V

THE DIGESTIVE SYSTEM

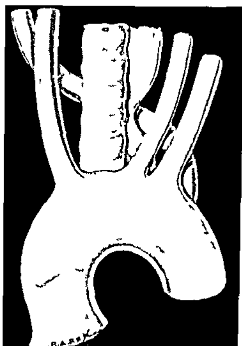
ESOPHAGUS

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anterior oblique view shows a 90 degree rectangular notch in the posterior aspect of the esophagus where it meets the upper edge of the arch This notch situated immediately above the aorta is made by the artery as it passes behind the esophagus It is seen less often in right anterior oblique



F g 8—D g m of r t ph g l b t ght s bclavı a te y l w g mp t m k n pl g (C te y of R J H a d B a J C R v confed med p n m 395-411 A g t 1955 from R a J H P th logy d Su ge y f the E ph gu [t b p bl sh d u d sp c s of V e l n Su g al Soc ety and A t a Soc ty f C acas])

esophagograms because the impression of the aberrant right subclavian artery on the esophagus is not strictly posterior but rather left posterior The position of the retroesophageal notch above the aorta is diagnostically important since it distinguishes this condition from other aortic malformations accompanied by definitely aortic esophageal constriction The differential x ray diagnosis is simple because the clear ness of the outline eliminates filling defects caused by ma

lignant neoplasms and because other conditions do not pro duce the characteristic angle in the notch Catheterization with opacification of the esophagus may be used in doubtful cases (Fig 79) and since the catheter itself acts as an opaque medium it is not necessary for the patient to run the risk of



Fig 79 —X y with th t za on f t ry d p fi t on f soph gu h w g h t ist ot h f be t ght bcl. t ry beh d pb g (Court y f R sa J H d B J C R e f d med. p m 2 395-411 Augu t 19 5 f om R sa J H P h l gy d S gery f th Esoph gu [to be p l h d d r pt f V la S g l Soc y a d A t Soc ety f C 1)

aortography with a contrast medium Only 4 of the 15 pa tients in this series had dy phagia and closer study showed that it was due to (1) a gastric neoplasm (2) magaesopha gus (3) a congenitally short and malformed esophagus and (4) esophageal scleroderma

Since symptoms are sometimes completely absent with an aberrant right subclavian artery adult or elderly patients in whom such an artery is associated with dysphagia should always be investigated for other possible causes of dysphagia

* [Ed ly Palmer in an article on the same subject (Ann Int. Med. 4?

particularly obvious when the esophagus is distended above and below Solid food pushes the free edge of the ring down thereby increasing the diameter of the opening If the diameter of the solid object is considerably larger than the opening elasticity is insufficient and the object is held above the ring Obviously the same mechanism causes dysphagia Extreme maximal diameters of the residual lumen are 3 38 mm With one exception diameters of symptomatic rings did not change during follow up of five years

Roentgenologically the ring is best seen with the patient horizontal face down and partly turned on the right side Even in this position no delay occurs in passage of usual barium water mixture and the ring may be missed unless the lower esophagus is sufficiently distended

Of 21 patients with dysphagia due to lower esophageal rings 11 were men only 3 of the 21 were under 50 A ring was seen in 64 patients with no dysphagia 10 were under 50 at examination Of 368 consecutive patients referred for gastrointestinal examination in whom a special effort was made to obtain spot films of the maximally distended lower esophagus 17 showed a ring 2 of these had dysphagia

Most patients can usually eat without difficulty and have only occasional obstruction usually with bread steak and occasionally potatoes Dysphagia is definitely related to maximal diameter of the ring All patients with the diameter under 13 mm had dysphagia and none with the diameter over 25 mm had this symptom In the in between group most patients had no dysphagia though an occasional instance occurred

In some patients the ring was definitely at the junction of the esophagus and a herniated portion of the stomach This makes differential diagnosis of small hiatus hernia difficult Whether the ring is always at the junction of the esophagus and herniated stomach is not known but it appears that some upward displacement of esophagus and stomach into the chest is always present Three patients with lower esophageal ring had Zenker s diverticula arising from the posterior wall of the lower hypopharynx at the junction with the cervical esophagus A hiatus hernia per se without esophagitis would not explain marked constant narrowing and dysphagia in symptomatic cases An annular contraction is easier to dif

ferentiate (Fig 81) It changes location in the esophagus whereas a lower esophageal ring remains stationary

The authors conclude that the ring represents a short annular segment of lower esophagus which for some reason cannot be distended as well as the structures above and below Treatment is less problematic than the nature of the ring As dysphagia will be present only if discrepancy exists between the known size of the ring and size and consistency of the bolus swallowed symptoms can usually be controlled if the patient understands the nature of the lesion and the necessity of eating slowly and of decreasing the size of the bolus Attempts at changing the narrowing pharmacologically and by bougienage have not been successful A very narrow ring may require plastic surgery

Lower Esophageal Web or ring an organic narrowing of the lower esophageal lumen may be present in many patients believed to have functional dysphagia according to Walter F Bugden and J Ernest Delmonico Jr[3] (State Univ of New York Syracuse) who report two illustrative cases



Fig 82—Obs rvat w th th k b m w b n t d g d b t pe t on dvi d f b tr ct g l ond hosp tal t s x m th lat (Co rt sy of B gde W F d D lm J E J J Th S g 31 1 18 J y 1956)

(3) J Th a c S g 31 1 18 J y 1956

During early stages dysphagia was most often related to attempted ingestion of meat and bread Drinking would often alleviate the low substernal discomfort and sensation of something stuck in the lower chest By careful mastication and dietary restriction severe symptoms were curbed for many years but dysphagia eventually became so severe that both patients had been taking only a liquid diet for the past year Both had gone from one physician to another seeking relief

In the first patient esophageal stricture was not diagnosed roentgenologically on first admission but repeat x ray study six months later showed a definite weblike structure 3 cm above the diaphragm and proximal to the esophagogastric junction (Fig 82) The web was not demonstrable until the esophagus above and below it was distended with thick barium The esophagus above the narrowing was not widened and proximally peristalsis functioned normally The web was smooth and 3 5 mm thick with central narrowing producing a shelflike symmetrical x ray shadow

Four esophagoscopies in the first patient and one in the second had been reported as normal

At thoracotomy the lesion was easily demonstrated by opening the esophagus longitudinally a few centimeters proximal to the obstruction Once identified the web was intussuscepted upward by the index finger inserted through a gastrotomy incision (Fig 83) The obstruction was located above the esophagogastric junction with 3 5 cm of normal appearing esophagus below it The narrow portion of the lumen in one case was 3 mm and in the other 5 mm In the second instance the base of the web presented a ringlike thickening After the lesion was exposed three pie shaped wedges of membrane were removed leaving intervening areas of mucosa at the base to prevent subsequent stricture Raw areas were sutured with interrupted silk and the stomach and esophagus were closed Patients were completely relieved of dysphagia on follow up seven and eight months postoperatively

The moderately rigid web about 3 mm thick was composed of hyperplastic squamous cell epithelium submucosa and muscularis similar to the normal lower esophageal wall

• [The lower esophageal ring is responsible for a real clinical entity

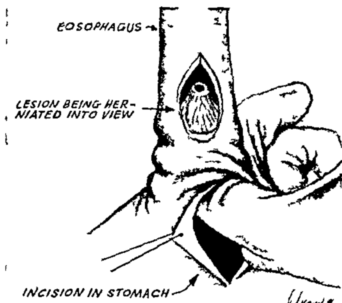


Fig 83 —W b tu su c pt d upw d w th l ft d x fi g st om h (Courtesy f B gd W F nd Delm c J E Jr J Thor c c S rg 31 1 18 J ary 1956)

but it is essential that the radiologic criteria laid down by Schatzki and Gary be strictly observed Many other indentations muscular or otherwise are seen at or above the gastroesophageal junction but their transient or irregular nature differentiates them from the bona fide lower esophageal ring

The nature of the ring is still controversial Bugden and Delmonico found esophageal mucosa distal to the ring thi is noteworthy since some have accepted the rather capacious lumen below the ring as evidence of diaphragmatic herniation of the stomach.—Ed]

Surgical Treatment of Achalasia of Esophagus is reviewed by Richard H Sweet[4] (Boston) Two types of achalasia can be differentiated About 75% of the patients have enormous esophageal dilatation above the distal segment without pain but with severe dysphagia Fluoroscopy shows peristalsis to be lacking At surgery the terminal esophagus is found to be small in diameter and its muscular wall abnormally thin in contrast to the enormously dilated thick walled portion above The other 25% have pain from esophagospasm early in the disease By x ray the esophagus is found to be only moderately dilated with fluoroscopy erratic hyperactive

(4) ew Engla d J M d 54 87 95 J 19 1956

peristalsis can be seen At operation the lower segment of the esophagu is found to be thickened owing to hypertrophy of the circular muscle fibers

Bougienage should be tried before surgery is undertaken but some patients do not respond to dilatation E ophago plasty a longitudinal incision through the entire length of the narrow lower segment followed by a circumferential closure of the opening eliminates the narrowed segment The lumen assumes a large diameter and dysphagia is com pletely and permanently relieved If the normal anatomic relation of cardia lower esophagus and esophageal hiatus is maintained the incidence of regurgitation from stomach into esophagus is reduced For circular muscle hypertrophy a single lengthwise incision through the thickened fibers (Heller esophagomyotomy) is sufficient

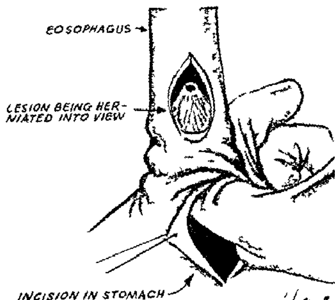
The 28 patients of the first type were treated by esophago plasty Two of these patients subsequently required radical proximal gastrectomy for hemorrhage and two died post operatively The 10 patients of the second type were treated by esophagomyotomy and none died

Of the 36 patients followed up 13 had no postoperative symptoms Occasional transitory delay in food passage was described by seven Severe pyrosis occurred in 4 moderate in 1 and slight in 10 Regurgitation of fluid into the pharynx was observed in 11 patients Bleeding from the upper gastro intestinal tract occurred in nine of undetermined source in two In three bleeding from acute gastritis was massive and endangered life Spasm at the distal end of the stomach may contribute to the frequency of gastritis in these patients

In 29 patients examined by fluoroscopy postoperatively the diameter of the esophagus had obviously decreased ow ing to surgical release of the obstruction Two patients had a duodenal ulcer but none had evidence of esophagitis or eso phageal ulcer Four had delayed emptying of the stomach 20 gained weight and 29 could do their usual work

The results were excellent in 19 patients 9 had only minor or occasional inconvenience 4 had satisfactory results 2 re quired partial proximal gastrectomy because of bleeding from gastriti and 2 required bougienage for relief of steno sis at the site of esophagoplasty All the poor results (four) were in patients treated by esophagoplasty

• [That two types of achalasia may be recogn zed clinically does not



[illegible]

but it [illegible] that the [illegible] [illegible] Schatzki and Gary [illegible] Many other [illegible] muscular [illegible] other [illegible] esophageal junction but the [illegible] [illegible] irregular [illegible] the [illegible] the [illegible] esophageal ring.

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(4) [illegible]

late those of cardiospasm and the clinician may be lulled into a false sense of security after a diagnosis of cardiospasm Further recurrences of cardiospasm typical or atypical are considered natural and early malignancy may be over looked until too late for effective therapy Exfoliative cytology performed annually should aid in detecting cancer complicating or masquerading as cardiospasm

• [Of all the technics of exfoliative cytology applied to the gastrointestinal tract the esophageal appears to be the most rewarding It is simple and may establish with unquestionable accuracy the diagnosis of malignancy even when roentgenography endoscopy and endoscopic biopsy fail —Ed.]

STOMACH AND DUODENUM

Gastric Secretory Response to Histalog One Hour Basal and Histalog Secretion in Normal Persons and in Patients with Duodenal Ulcer and Gastric Ulcer was studied by Joseph B Kirsner and Harold Ford[6] (Univ of Chicago) Preliminary observations have indicated that histalog (3 beta aminoethyl pyrazole) (Lilly) an analog of histamine stimulates gastric secretion with less side effects than histamine

After basal collections for an hour 0 5 mg /kg body weight histalog was administered subcutaneously and aspirations continued for another hour Data were obtained on 584 normal persons (304 males and 280 females) 231 patients with duodenal ulcer (173 males and 58 females) and 22 patients with gastric ulcer (15 males and 7 females)

Histalog significantly increased gastric secretion in all patients Output of hydrochloric acid after histalog exceeded corresponding response to histamine in most patients but differences were not clinically important except possibly in study of suspected achlorhydria when the most potent gastric stimulation is desirable

Anacidity throughout the entire basal period was observed in 22% of normal males and 30% of normal females Outputs of hydrochloric acid after histalog were much higher in normal males than females but proportionate increases above basal levels were about similar in the two sexes In the same person basal and histalog stimulated secretions were defi

(6) J Lab & Cl Med 46 307 311 August 1955

necessarily mean that the types are qualitatively different. Cardiospasm (or achalasia) is a diffuse disorder affecting the neuromuscular mechanisms controlling esophageal peristalsis and tone If damage is partial an irritable esophagus only mildly dilated and given to painful spasm, is found With more extensive damage even un co-ordinated spasm disappears and the baglike picture of megaesophagus results

I am convinced that if dilation of the distal narrowed segment is carried out properly and sufficiently early the need for surgery in cardiospasm will all but disappear Proper dilation is not the passing of mercury filled bougies which do nothing but dilate the narrow segment temporarily The muscle of this segment must be torn by forcible distention by means of a bag inflated under pressure or a Starck dilator Only sufficient damage to the muscle can prevent the distal narrow segment from resuming its state of perpetual nonrelaxation —Ed]

Diagnosis of Esophageal Carcinoma by Exfoliative Cytology Including Two Cases of Cardiospasm Associated with Carcinoma of Esophagus Melvin I Klayman (Univ of Chicago) examined 40 patients with suspected esophageal pathology

TECHNIC —The patient sipped and swallowed 100 200 cc Ringer s solution which was recovered via an intragastric tube The tube was withdrawn to the cardia and various levels of the esophagus irrigated If persistent resistance was encountered in passing the tube irrigations were conducted at this level The collected material was immediately placed in plastic tubes immersed in ice and centrifuged for three minutes within five minutes of aspiration The sediment was smeared on glass slides and fixed in standard alcohol ether fixative Rubin s modification of Papanicolaou staining was used Average time required for study of each patient was 20 minutes

There were no indeterminate reports malignant cells were reported as either present or absent Of the 40 patients 20 had malignant growths proved histologically and by operation and 20 had benign esophageal lesions Of the 20 malignancies 19 were correctly diagnosed by exfoliative cytology In the single case misdiagnosed the mucosal surface was intact except for a minute fissure covered by a membrane Exfoliation of malignant cells into the lumen is necessary if the cells are to be recovered

Exfoliative cytology can detect carcinoma of the esophagus accurately even when radiology and esophagoscopy fail Diagnosis may be made before motility is disturbed or other gross abnormalities detected By earlier diagnosis the desired increased patient cures may be attained

In cardiospasm the incidence of malignant degeneration of the esophagus is increased Symptoms in carcinoma simu

(5) A n Int Med 43 33 44 J ly 1955

patients are achlorhydric and 10 15% are hypochlorhydric (free HCl under 30 units after histamine) gastrointestinal examinations were done yearly on 1 747 persons over age 50 years with achlorhydria hypochlorhydria and pernicious anemia Among these patients 55 gastric polyps and 19 gastric cancers were found Only four who had cancer had symptoms which might have led them to seek diagnosis earlier Nine (47%) had negative lymph nodes at time of surgery contrasted with 20% in routine surveys Incidence of gastric cancer in the achlorhydric group was 3 2 times the expected incidence for persons in the same age group in the hypochlorhydric group 2 6 times and in the pernicious anemia group 18 3 times Average increase in incidence in precursor groups is 3 8 times the national incidence

In an independent seven year study by the cancer detection center achlorhydria or hypochlorhydria was found in 1 769 (25%) of 7 074 supposedly well people examined and tested for free HCl using one dose of histamine phosphate (0 5 mg) Nineteen gastric cancers were also discovered in this group No case of gastric cancer would have been missed if all screening factors except achlorhydria or hypochlorhydria had been omitted No gastric cancer was found in the normochlorhydric group but one may have been missed because normal gastric acidity was reported one year before actual pick up Incidence of gastric cancer in this group screened by age and achlorhydria hypochlorhydria factors is 5 2 times higher than that expected in the general population of similar age Correction to include time (patient years) reveals an incidence of 423 1/100 000 persons over age 50 years per year or 7 1 times the expected over all national rate for this age group

Routine gastric x rays of the entire adult population are unfeasible and unobtainable with application of age and achlorhydria hypochlorhydria as screening criteria attention can be concentrated on a smaller more highly susceptible segment of the population Detection of 38 gastric malignancies among 3 516 subjects (1 8%) in the two series demonstrates the value of this method

Members of the susceptible group should be examined as follows (1) Pernicious anemia patients should have a gastrointestinal series study every six months (2) Achlorhydric

nitely correlated Anacidity after histalog was present in 4% of both normal males and females more frequently after age 50

None of the patients with duodenal ulcer had anacidity after histalog stimulation In patients with gastric ulcer volumes of basal secretion approximated normal values whereas concentrations of hydrochloric acid were slightly less than normal Three patients had continuous basal anacidity but all patients showed acid after histalog stimulation

In doses of 0 01 mg/kg body weight histamine almost invariably caused an uncomfortable flushing and throbbing sensation in the head In more than 90% of the patients headaches developed which in about 50% were severe Weakness and nausea occurred in 20% and 5% had mild shock with transient unconsciousness

In contrast among 2 000 patients who have received histalog 20% had a sense of flushing but only 1% reported actual discomfort Three per cent had headaches 1% weaknes nausea and faintness and 0 2% transient syncope These findings indicate that histalog in quantities 50 times larger than those of histamine is about 25 times less toxic In patients receiving both compounds at different times preference for histalog was unanimou

Outputs of acid after histalog were largest in patients with duodenal ulcer but the response did not differentiate patients with duodenal ulcer from those with gastric ulcers or from controls as clearly as did the one hour basal secretion The 1 hour basal secretion is an index of the gastric secretion of the individual and parallels the more elaborate but less practical 12 hour nocturnal gastric secretion

• [On the basis of these studies should histalog replace histamine in the clinical study of gastric secretion Before this question can be answered the effects of histalog should be compared with the result obtained by Hunt and Kay s maximal histamine stimulation technic (1955 56 YEAR BOOK p 482) —Ed]

Value of Achlorhydria as Screening Test for Gastric Cancer 10 Year Report of a program involving over 12 000 persons is presented by Claude R Hitchcock W Albert Sullivan and Owen H Wangensteen[7] (Univ of Minnesota) Because current surveys show that 70 75% of gastric cancer

(7) G troe te log 9 6 1 63 O t be 1955

patients are achlorhydric and 10 15% are hypochlorhydric (free HCl under 30 units after histamine) gastrointestinal examinations were done yearly on 1 747 persons over age 50 years with achlorhydria hypochlorhydria and pernicious anemia Among these patients 55 gastric polyps and 19 gastric cancers were found Only four who had cancer had symptoms which might have led them to seek diagnosis earlier Nine (47%) had negative lymph nodes at time of surgery contrasted with 20% in routine surveys Incidence of gastric cancer in the achlorhydric group was 3 2 times the expected incidence for persons in the same age group in the hypochlorhydric group 2 6 times and in the pernicious anemia group 18 3 times Average increase in incidence in precursor group is 3 8 times the national incidence

In an independent seven year study by the cancer detection center achlorhydria or hypochlorhydria was found in 1 769 (25%) of 7 074 supposedly well people examined and tested for free HCl using one dose of histamine phosphate (0 5 mg) Nineteen gastric cancers were also discovered in this group No case of gastric cancer would have been missed if all screening factors except achlorhydria or hypochlorhydria had been omitted No gastric cancer was found in the normochlorhydric group but one may have been missed because normal gastric acidity was reported one year before actual pick up Incidence of gastric cancer in this group screened by age and achlorhydria hypochlorhydria factors is 5 2 times higher than that expected in the general population of similar age Correction to include time (patient years) reveal an incidence of 423 1/100 000 persons over age 50 years per year or 7 1 times the expected over all national rate for this age group

Routine gastric x rays of the entire adult population are unfeasible and unobtainable with application of age and achlorhydria hypochlorhydria as screening criteria attention can be concentrated on a smaller more highly susceptible segment of the population Detection of 38 gastric malignancies among 3 516 subjects (1 8%) in the two series demonstrates the value of this method

Members of the susceptible group should be examined as follows (1) Pernicious anemia patients should have a gastrointestinal series study every six months (2) Achlorhydric

hypochlorhydric persons should have gastrointestinal x rays every 9 12 months (3) Gastric polyp patients should have early removal of polyps and gastric x rays every 9 12 months The silent interval of gastric cancer averages 18 24 months With a long range program of yearly re examination of more highly susceptible groups many more gastric cancers can be detected in the presymptomatic phase

A B O Blood Groups and Gastric Acidity K H Køster Erik Sindrup and Vagn Seele[8] (Copenhagen) compared the distribution of A B O blood groups in patients with carcinoma of the stomach and gastric or duodenal ulcer with that of healthy persons Of 413 with gastric carcinoma 34 1% were of group O 51 3% of group A and 10 7% of group B 3 9% were of AB type The relative excess of group A is 7 3% higher than in the control group Of 301 patients tested for gastric acidity 195 were achlorhydric and in 106 free HCl was detected Of those with histamine or insulin achlorhydria 56 4% were of blood group A with group O correspondingly low (33 2%)

The frequency of blood group A among 1 047 patients with peptic ulcer was 39 3% (controls 44 0%) The frequency of groups A and AB was also lowered and this deficit was reflected in the increase in group O to 48 7% (controls 40 6%) Group O was more prevalent in patients with duodenal (50 2%) than in those with gastric ulcer (46 3%) and there was a corresponding fall in group A

The amount of free acid in the stomach ranges from the highest to the lowest as follows duodenal ulcer gastric ulcer normal cancer of the stomach with free acid and cancer of stomach with achlorhydria In this study the shift from conditions associated with the least to the greatest production of acid was accompanied by an increasing frequency of blood group O and a decreasing frequency of blood group A The frequency of blood groups B and AB was not similarly reversed

• [This article is but one of several reporting with remarkable consistency the trend of blood group distribution here described for cases of gastric cancer on one hand and for peptic ulcer on the other—Ed]

Granuloma with Eosinophils Benign Inflammatory Fibroid Polyps of Stomach must be considered in differential diagnosis of filling defects in x rays of the stomach The

(8) Lancet 2 52 55 July 9 1955

lesion involving mucosa and submucosa forms a fairly well circumscribed more or less elevated mass of variable size Histologically it is characterized by rather loose fibrous tissue partly in faintly lobular arrangement with a cellular infiltrate that is dominated by eosinophils For this reason Leo G Rigler Leo Blank and Robert Hebbel[9] (Univ of



Fig 84—X y f d tal th d f st m h m d with c mp es on und th fl r scope A mod at ly l b l ted h ply def d l fill g d fect be een i th a trum. (C t y f R gl L. G t l R d logy 66 169 176 F bru ty 1956)

Minnesota) prefer the designation of granuloma with eosinophils

The nine patients described were aged 37 83 all but one were over 51 Only four had symptoms referable to the gastrointestinal tract which might conceivably be attributed to the lesion In two symptoms simulated those caused by duodenal ulcer One had severe and two others had moderate anemia Five patients were women

(9) R d logy 66 169 176 F bru y 1956

All the lesions originated in the antrum and were in the mucosa and submucosa although they presented as polypoid masses Many showed shallow ulcerations especially at the apex these were recognizable by x ray in two De p te high incidence of carcinoma associated with this lesion in reported cases and in two of the authors patients it is generally accepted that the origin is inflammatory although pathogenesis is not fully understood

Roentgen diagnosis in seven of the patients was benign polyp One polyp was thought to be benign tumor and one was reported as carcinoma which was present Granuloma was not distinguishable from the defect caused by the neoplasm Clinical and roentgenologic similarities between such granulomas and benign adenomatous polyps of the stomach are notable The most characteristic x ray difference is extremely sharp definition of the margins of the filling defect In six cases spot films were obtained with pressure in four of these a round filling defect in one an oval and in one a moderately lobulated defect (Fig 84) was seen Although adenomas may be sharply defined there is usually a slight haziness of margins defects are of varying shapes and may be lobulated

It is recommended that when roentgenograms reveal the characteristic filling defect preparation be made for frozen section examination at operation and when microscopic study establishes a granuloma local excision only should be performed

• [The authors provide no information concerning the differential white cell count In an article on the same subject Marki (Schweiz med. Wchnschr 84 1269 Nov 6 1954) mentions that eosinophilia in the blood occasionally provides a diagnostic lead if gastric polypoid lesions are discovered radiologically A few eosinophilic granulomas in the antrum of the stomach apparently are less sharply circumscribed and more infiltrative than those seen by Rigler s group —Ed]

Role of Gastric Secretions in Activation of Peptic Ulcers by Corticotropin (ACTH) Basil I Hirschowitz David H P Streeten H Marvin Pollard and Henry A Boldt Jr[1] (Ann Arbor Mich) gave 25 units of corticotropin gel intramuscularly every 12 hours for six days to six male students aged 19 25 and determined the effect on gastric secretion by measuring the volume pH chloride content concentration of free acid pepsin concentration and viscosity of gastric

(1) J A M A 152 27 32 May 7 1955

contents In addition urinary and plasma pepsinogen were estimated

Corticotropin given to five normal men with repeatedly normal gastrointestinal x rays caused increased urinary excretion of 17 hydroxycorticoids and decreased circulating eosinophils in all The viscosity of the gastric juice and amount of visible mucus were distinctly decreased Concentration of pep in in the gastric juice increased moderately and progressively mean acid concentration increased slightly but volume decreased slightly in all subjects The total amounts of both acid and pepsin secreted thus remained relatively constant throughout the study Plasma pepsinogen concentration was unchanged Urinary excretion of pepsinogen constant during the control period ro e steeply on the first day of corticotropin administration and remained elevated until the hormone was discontinued

In the sixth subject a duodenal ulcer appeared while he was receiving corticotropin Preceding the exacerbation there was no significant increase in the secretion of acid or pepsin by the stomach The highest concentrations were well within the normal range both before and on the third day of corticotropin administration only 40 hours before the onset of ulcer symptoms Analysis of the literature also suggests that the time relationships between corticotropin administration and ulcer exacerbation are such that ulcer exacerbation whether occurring naturally or during corticotropin administration may not be preceded by increased gastric secretion of acid and pepsin Perhap the increased secretion is the result of duodenal ulceration rather than the cause

In the ulcer patient the viscosity of the gastric juice wa reduced to less than that of water at the onset of symptom None of the other subjects showed such a marked change and the fall in viscosity and visible mucus content may have been causally related to reactivation of the ulcer

In the sixth subject increased urinary excretion of pepsinogen did not appear until five days after the first symptoms of ulcer At this time the pep in content of gastric juice was falling rapidly Such a divergence of gastric pepsin and urinary pepsinogen indicates that urinary pepsinogen excretion could be a misleading index of gastric secretion Urinary pepsinogen excretion in any one individual is fairly con

stantly related to pepsin concentration in fasting gastric juice but no predictable relationship holds for all individuals Under conditions of change such as adrenal stimulation the relationship is disrupted The immediate and sustained increase in pepsinogen excretion results mainly from renal rather than gastric changes renal clearance of pepsinogen being greatly increased by corticotropin and various adrenal steroids

Addison s Disease and Peptic Ulcer Frank L Engel (Duke Univ) presents the case of a 49 year old woman with Addison s disease to *illustrate the permissive role played by the adrenal cortex in the etiology of peptic ulcer* During the initial periods of her illness gastrointestinal symptoms were prominent but no abnormalities were found by x ray No free acid was found in the stomach on fasting or after histamine The patient responded to 25 mg cortisone daily and implantation of a pellet of desoxycorticosterone acetate She was completely rehabilitated but three years later gastrointestinal symptoms again developed and a small prepyloric ulcer was found Twenty nine units of free gastric acid were found after histamine Since she was on a fixed dose of cortisone and her adrenal glands were incapable of further secretion of hormone *the development of the ulcer cannot be related to an enhanced secretion of adrenal hormone*

Any concept relating the adrenal cortex and peptic ulcer must take into account the following facts Peptic ulcer is rare and gastric secretion is depressed in untreated adrenal insufficiency Gastric secretory activity is increased and gastric or duodenal ulcers occasionally occur or are reactivated in patients with Addison s disease who receive maintenance cortisone therapy In patients without Addison s disea e given ACTH or cortisone peptic ulcers develop or recur and delayed enhanced gastric secretory activity is noted Gastric secretory activity promptly increases in re ponse to physical and emotional stress in many patients

These facts correspond with tho e which have related the response to nonspecific stress and the adrenal cortex and are consistent with the view *that the adrenal cortex plays a permissive role in the activation of ulcer* Thus adrenal hormone pre umably mu t be available if ulceration is to be initiated

(2) J Cl E doc ol 15 1300 1306 Octobe 1955

but the hormone is not in itself the cause With excess hormone present as in either endogenous or exogenous hyperadrenocorticism the gastric and duodenal mucosa may be more responsive to potentially noxious stimuli which otherwise would not be sufficient to initiate ulceration With no change in adrenal hormone secretion (as in the patient described) certain stimuli may be sufficient by themselves to initiate peptic ulceration

• [According to Seymour Gray who has observed seven cases of the type here described the patient with Addison s disease not only may get peptic ulcer when he is treated with cortisone but may be unusually susceptible to this complication Ulcers may develop when such patients are maintained on doses of cortisone too small to affect gastric function in normal subjects —Ed]

Associated Gastric and Duodenal Ulcers Among 347 patients operated on for peptic ulcers H Daintree Johnson[3] (London) encountered 32 with both gastric and duodenal lesions a factor common to all was gastric retention To these he added 103 collected cases Of the 135 patients 111 were men aged 26 84 (average 53) In 30 both ulcers were discovered on first x rays In seven neither ulcer was discovered by x ray but both were present at operation Operations for acute perforations of peptic ulcers had been performed on 21 before gastric ulcer was discovered Treatment for duodenal ulcer had been carried out in 70 for several years before x rays or operation revealed gastric ulcer In only seven cases was gastric ulcer seen first In all these duodenal ulcer presented as a healed scar at operation so it may have actually preceded the gastric ulcer

All night secretion tests clearly showed that asociated ulcers occur in patients of hypersecreting duodenal ulcer type rather than in the hyposecreting gastric ulcer type An unusual degree of gastric retention was almost the rule when combined ulcers were present Stenosis was mentioned in surgical notes in 33% and reported by the radiologist in another 22% Clinical evidence of gastric retention was found in another 9% making a total of 64%

The most frequent finding at operation was of a healed stenosed duodenal lesion and an active often huge and sometimes bleeding gastric ulcer Only 8% of gastric ulcers were healed whereas 70% of duodenal ulcers were inactive

(3) S g Cy & Ob t 10 287 292 M rch 1956

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(2) J Cl E doc t 15 1300 1306 O t ber 1955

tion 8 had typical acute erosive gastritis which was moderately severe in 5 Large portions of residual aspirin were found but they were almost always coated by a thick capsule of dense mucus Of 20 patients who received soluble calcium aspirin 18 had no mucosal reaction 2 had a mild reaction not definitely classified as abnormal

About 1 in 20 among 300 persons representing an average cross section of the community stated that aspirin caused dyspepsia heartburn sometimes nausea and occasionally epigastric discomfort Of 318 patients with peptic ulcer approximately a third (110) were aware that aspirin could be taken only at the risk of a bout of dyspepsia and some avoided it entirely for that reason Of 83 patients with peptic ulcers which relapsed after long remission 14 (of 34) with gastric ulcer and 19 (of 49) with duodenal ulcer admitted taking aspirin less than 24 hours before recurrence Fifteen patients (11 women) with chronic dyspepsia who were habitual takers of aspirin were cured of symptoms by its withdrawal

Of 166 patients with hematemesis (117 men) about a third had taken aspirin within six hours of hemorrhaging In those whose hematemesis was based on some acute lesion the incidence of taking aspirin was nearer 50% In 21 patients histories indicated that aspirin was the major factor in precipitating the hemorrhage which occurred with epigastric discomfort and heartburn shortly after taking two aspirin tablets on an empty stomach Of 44 patients with perforated peptic ulcer only 1 admitted taking a pirin within six hours of acute duodenal perforation In a control series approximately 1 in 20 took aspirin within six hours of admission

These findings indicate that aspirin may act as a severe gastric irritant in some people The basic lesion is an acute erosive gastritis sometimes of surprising severity It was believed that aspirin hematemesis was in most of the authors patients based on acute erosive gastritis whether or not peptic ulceration was al o present The conclusion is that aspirin should never be given to patients with peptic ulcer or to those who have any gastric intolerance however mild Calcium aspirin does not have this irritant effect unless it has deteriorated through standing and can be safely prescribed e pecially in soluble form

• [Aspir n being the common drug that it is it may be as easy to obtain

and scarred Both ulcers were active in 22% and both healed in 3%

In 16 additional patients gastric retention due to causes other than duodenal ulcer was complicated by gastric ulcer Five patients were encountered who had had vagotomy all had healed duodenal ulcers with much scarring and gross delay in gastric emptying

When gastric ulcer develops as a complication of gastric retention it does not behave as other gastric ulcers do but tends to become very large and deep and resistant to treatment It is also particularly prone to massive hemorrhage In 13 patients who underwent emergency gastrectomy for active bleeding it was the gastric ulcer that was bleeding in each instance

When both gastric and duodenal ulcers are present operation suitable for the hypersecreting duodenal ulcer patient is required moderate resection recommended for gastric ulcer alone would be inadequate As an alternative to radical gastric resection more limited resection may be combined with vagotomy 265 patients with duodenal or combined duodenal and gastric ulcers so treated have been followed one to seven years without recurrence

• [Mr Norman Tanner of England has also commented on the tendency of gastric ulcer to appear in those who have had duodenal ulcer for a long time This association and Dr Johnson s emphasis on the relationship of gastric retention to formation of gastric ulcer lend considerable support to Dragstedt s theories Many gastric ulcers however appear to originate *de novo* without any antecedent acid peptic disorder and unaccompanied by any detectable evidence of gastric retention —Ed]

Aspirin and Ulcer A Muir and I A Cossar[4] suspect aspirin as a cause of gastric complaints In comparative caffeine citrate test meals in 20 patients with peptic ulcer aspirin (two 5 gr tablets) tended to increase gastric acidity and evidence of gastric irritation In five patients blood staining of specimens was observed only during the aspirin test

Of 20 patients who received two 5 gr commercial aspirin tablets about two hours before gastrectomy 12 had acute gastritis macroscopically In three it was severe and most marked in the pyloric antrum and on the lesser curvature In one half an aspirin tablet was deeply embedded in the mucosa of the greater curvature When removed a lesion resembling acute peptic ulcer was visible Of 20 patients who received specially prepared hard aspirin tablets before opera

(4) B M J 2 712 July 2 1955

route Hypoxia may be common to a number of clinical conditions in which peptic ulcer is a complication viz vascular diseases polycythemia vera and shock Hypercapnia could possibly accelerate hydrochloric acid elaboration by the gastric mucosa because of increased local production of carbonic acid by carbonic anhydrase in the parietal cells

• [The *observed* relationship is interesting the suggested explanations for a *causal* relationship face too many objections to be tenable Lowell and his associates (New England J Med 254 123 Jan 19 1956) have also found a high correlation of obstructive emphysema and acid peptic disorders but these authors find the ulcer in the duodenum and smoking is regarded as an etiologic culprit.—Ed]

Dietetic Treatment of Peptic Ulcer Because the value of a special diet was never demonstrated in a controlled series R Doll Peter Friedlander and Frank Pygott[6] (London) compared the effects of two different diets on (1) the rate of healing of gastric ulcers in 64 hospital patients and (2) the frequency of recurrent symptoms and unhealed ulcers in 130 outpatients with gastric or duodenal ulcers

A standard ulcer diet was used The contrasting diet was the normal hospital diet without fried food and included snacks at 10 a m and 9 p m The patients were comparable before treatment Those previously treated were excluded from the trial all others were randomly assigned to a treatment group Results were assessed by changes in the radiographic ulcer niche weight gain and duration of symptoms

In the hospitalized patients more ulcers were completely healed in one month and weight gain was greater among patients on the almost normal diet than on the ulcer diet but the differences were not statistically significant However the patients on the ulcer diet were more improved subjectively All the outpatients were given alkaline powder for pain in addition to dietetic advice Treatment failed in more patients on the ulcer diet than on the normal diet but again fewer patients on the ulcer diet had symptoms The percentage pain free throughout the study and the percentage whose ulcer healed were closely similar in the two dietary groups

The rate of healing of a peptic ulcer is not materially affected by limiting the diet to bland foods Even fried foods are not harmful

• [Studies such as this are long overdue since the dietotherapy of gastrointestinal disorders is mainly traditional and not based on valid study On

(6) Lancet 1 5-8 Jan 7 1956.

a history of aspirin ingestion as it is to obtain a history of some sort of emotional upset in the hours preceding a gastrointestinal episode Elaborate control series and checks are therefore necessary before definite conclusions can be reached Furthermore if patients take aspirin there usually is some reason a headache or cold that may be more to blame for activation of ulcer symptoms than the aspirin It is even possible that patients who have already started to bleed take aspirin because the blood loss is making them feel poorly

Sometimes in an effort to prove that aspirin hemorrhage is a real entity some remarkable statements appear in print viz She knew that aspirin usually caused nausea or actual vomiting and had always avoided it in the past (Brit M J 2 1532 Dec 24 1955) Although the evidence is still fairly tenuous it would seem the part of wisdom not to give aspirin to patients with peptic ulcer

The soluble inorganic salts of aspirin are rarely used in the United States today —Ed]

Coincidence of Benign Gastric Ulcer and Chronic Pulmonary Disease John M Weber and Lucien A Gregg[5] (V A Hosp Aspinwall Pa) reviewed the records of all patients with benign gastric ulcer from 1948 to 1953 The benign nature was confirmed by autopsy operation or complete healing on serial x rays

Chronic pulmonary disease refers to a clinical state without specific pathogenesis characterized by diffuse lung damage especially emphysema and fibrosis accompanied by long standing symptoms of respiratory dysfunction Diagnosis was based on history physical findings and roentgenographic and ECG evidence Significantly active tuberculosis and such focal pulmonary disease as carcinoma and abscess were not encountered Typical physical signs were restricted thoracic excursions barrel chest hyperresonance diminished breath sounds and sibilant rales

Pulmonary disease was found in 30 of the 70 patients with benign gastric ulcer a coincidence of chronic pulmonary disease and benign gastric ulcer of 43% Degree of pulmonary involvement was severe in 24 and 5 of these had cor pulmonale No comparable frequency was found in patients with duodenal ulcer In the hospital population at large incidence of chronic pulmonary disease was only 10%

There is no satisfactory explanation why chronic lung disease should follow gastric ulcer The converse however may be true Disturbance of gas exchange in the lungs and consequent hypoxemia perhaps act as a stressful stimulus leading to gastric hypersecretion through the adrenocortical

(5) A I t Med 4 1026-1030 May 1955

duced consistently for 30 270 minutes Atropine methantheline (banthine®) bromide and scopolamine N butylbromide were effective in some patients Homatropine methylbromide was ineffective

Optimal effective dose of each of these drugs varied considerably from one patient to another the drugs cannot be compared therapeutically unless the dose is adjusted for each patient according to accompanying side effects Several times the dose recommended for the active drugs studied may be needed to suppress basal gastric secretion Optimal effective dose is determined by starting each patient at the recommended dose and increasing each successive dose by one increment until blurring of vision occurs The dose continued is one increment below the blurring dose

Optimal Effective Dose of Anticholinergic Drug in Peptic Ulcer Therapy was studied by David C H Sun and Harry Shay[8] (Temple Univ) Duration of suppression of gastric acidity to pH 4 5 or higher was selected as the main criterion for judging significant antisecretory potency The dose adopted—optimal effective dose (OED)—was one increment below that which produced uncomfortable symptoms of parasympathetic inhibition The effect of a single OED of four drugs given intraduodenally was determined in 46 experiments on 22 patients with chronic duodenal ulcer secreting acid gastric juice continuously Tricyclamol (elorine®) methylsulfate was effective in suppressing basal gastric acidity to pH 4 5 or higher in all 16 patients tested mepiperphenidol (dartine®) bromide in all 13 tested propantheline (probanthine®) bromide in 11 of 12 and belladonna tincture in only 2 of 5 Duration of effects was 30 240 minutes Although the intensity of secretory inhibition after a single OED of these drugs varied from patient to patient results were reproducible in the same patient None of the drugs produced suppression of gastric acidity to pH 4 5 or higher without accompanying dryness of the mouth although the degree of dryness was not constant on a given dose in the same patient The dose must be tailored to each patient and not administered according to body weight or any recommended uniform dose

On the day after continuous oral administration of tricy

(8) A M A Arch Int Med 97 44 45 Ap 1, 1956

the other hand the results reported cannot be accepted without reservations Radiologic evaluation of the degree of ulcer healing is only approximately accurate weight gain is a relatively poor criterion of response to therapy by the patient with an uncomplicated ulcer and the high proportion of gastric ulcer cases studied does not represent the relative incidence of gastric and duodenal ulcer at least as seen in the United States —Ed]

Relative Effectiveness of Anticholinergic Drugs on Basal Gastric Acidity was studied in 116 experiments on four patients with duodenal ulcer by David C H Sun Harry Shay and Joseph L Cimmerer (Temple Univ)

METHOD —*All patients were conditioned by repeated intubations before studies were started They fasted about 14 hours and received no medicaments the day before the test Two Rehfuss tubes were introduced under fluoroscopic observation the tip of one into the antrum of the stomach and the tip of the other into the metaduodenum Simultaneous continuous aspiration was maintained through each tube The drug was dissolved in 10 cc isotonic NaCl solution and introduced through the duodenal tube To estimate spontaneous fluctuation of basal gastric secretion three control studies five hours long were done on each patient on different days and a fourth study was done when evaluation of a series of drugs was completed Since none of the drugs produced anacidity without accompanying dryness of the mouth and since the degree of dryness was not constant for a given dose in the same patient the dose adopted was the maximal amount that could be used without causing blurring of vision*

In the same patient range of hourly variation in volume on any one day was as great as 100% and that of free and total acid output as great as 150% The coefficient of variation of hourly volume and free and total acid output from hour to hour on the same day was as great as 29 60 and 55% and from day to day in the same hour period 31 65 and 60% respectively Statistical analysis of control studies indicated that variation in hourly volume and in free and total acid output among patients was significantly greater than on different occasions in the same patient

Antisecretory potency of 10 anticholinergic drugs was judged by production of pH 4 5 or higher in the gastric secretion With the use of a dose one increment below that which produced blurring vision propantheline (pro banthine*) bromide both regular and long acting mepiperphenidol (darstine*) bromide meth copolamine (pamine*) bromide and elorine* sulfate were found to be effective in all patient in that periods of anacidity of pH 4 5 or higher were pro

(7) J A M A 158 713 18 July 2 1955

Effectiveness of the OED (250 mg) of tricyclamol methyl sulfate and its superiority over the recommended dose (50 mg) in one patient for inhibiting gastric secretion induced by emotional stress (a disturbing interview with the psychiatrist) illustrate further the value of the OED (Fig 85) Studies on the effect of anticholinergic drugs on gastric secretion induced by insulin hypoglycemia showed that the OED of an effective drug could produce pronounced inhibition of the late phase (adrenal phase) of gastric secretion in some patients

Absence of untoward side effects following prolonged administration of the OED of these drugs makes this dose practical for clinical use and may offer an approach to a regimen designed to prevent ulcer recurrence When administered after a meal the dose can be one increment higher than if given before meals

• [Many therapeutic pearls are provided by these two studies The clinician s suspicion that anticholinergics which do not produce side effects are apt to affect gastric pH but little is confirmed The wide range of susceptibility of different individuals to the same drug emphasizes the need of a tailored dose One objection must however be raised with respect to the method of study The drugs tested were given intraduodenally a method of administration which with respect to efficacy of anticholinergics occupies a position approximately midway between oral and intramuscular administration. Such tests as depended on duodenal instillation of the drug consequently cannot be considered truly representative of the clinical use of anticholinergics —Ed]

Peptic Ulcer in General Practice David I Finer and John Fry[9] (London) review the incidence morbidity and response to treatment of peptic ulcer in two practices totaling almost 10 000 patients The patients occupations varied but were chiefly clerical and industrial There was neither real poverty nor excessive prosperity Diagnosis was made only if radiologic evidence corroborated a history of ulcer dyspepsia

Most previous reports have been based on hospital figures which may not be correct since they include only cases referred for consultant help Although referral rates depend on many factors patients with the more severe cases tend to be hospitalized while those with the milder cases remain under the sole care of the family doctor In addition the referral rate depends on the general practitioner s attitude toward the disease and his facilities for diagnostic and pathologic study

Of 9 975 patients in the practices 177 had either a gastric

(9) Brit M J 2 169 17 July 16 1955

clamol methylsulfate to seven patients reduction in volume and in free and total acid output of basal gastric secretion occurred Mean hourly volume was 57 7% of that in the control period mean hourly free acid 28 1% and mean hourly total acid output 21 9%

Hourly pH studies of gastric contents throughout the day and night in eight patients with ulcers on a diet of milk cream and skim milk powder mixture alone and combined

F g 85 —The pH al es of gastr cont s d g mot n l tr s pl one " ec mme d d d (50 mg) and m t onal tr phas e e OED (50 mg) of t cycl m l methyl lfate (C u t sy f Su D C H nd Sh y H A M A A h I t M d 97 442-452 April, 1956)

with a mixture of aluminum hydroxide and magnesium trisilicate (AMT) and/or one recommended dose of tricyclamol methylsulfate or mepiperphenidol bromide failed to control gastric acidity satisfactorily Use of optimal effective doses of tricyclamol methylsulfate and mepiperphenidol bromide produced satisfactory results in four patients The pH of gastric contents remained at 4 5 or higher for variable periods during day and night Night secretion was controlled by giving an additional optimal effective dose of the drug at 3 30 a m

to seal the perforation in five cases operation was done with recovery in all Peritoneal fluid was drained in five other cases during the second week after perforation Including these 10 cases surgery was required in 22 of the total 200 cases in 21 of which the perforations were of chronic ulcers

Among the chronic ulcer patients mortality of perforation was 14% including moribund patients Follow up was possible on 95% of the survivors and gastric histories of 153 patients were studied Recurrent ulcer developed in four fifths of those with chronic ulcers almost half required subsequent operation and three died Only three of those with acute ulcer have had any symptoms and these were mild and easily controlled medically

In a reported series (Gilmour) of 119 perforated acute ulcers closed by suture there were no fatalities It is clear therefore that the life of a patient with a perforated acute ulcer is hardly at risk whether he is treated by aspiration or by suture The incidence of recurrent ulcer however is the decisive factor and results indicate that recurrence is much less frequent after aspiration Closure by suture distorts the stomach wall introduces foreign bodies and interferes with local blood supply The result is a vulnerable scar liable to lead to recurrence of ulcer (in 25%) Among nine patients operated on through diagnostic error five had perforations of acute ulcers In two of these recurrent ulcers developed after suture and one underwent surgical treatment for it

The situation with regard to perforated chronic ulcer is quite different Neither operative suture nor gastric aspiration is safe enough in these cases Partial gastrectomy is the treatment of choice

Study of Unselected Series of Postgastrectomized Patients Ralph D Eichhorn and Ralph Bowen Jr (Houston) followed up 40 male veterans who had undergone subtotal gastrectomy by various surgeons in all parts of the United States Preoperative diagnoses were duodenal ulcer in 35 and gastric ulcer in 5 Surgery was performed between 1944 and 1951 and from the pathology reports surgery was adequately indicated and the procedure was that preferred for the condition found at operation

The impression that surgeons in large teaching centers

(2) Am J G t oent 1 24 649 654 Dec mbe 1955

or a duodenal ulcer an incidence rate of 17 7/1 000 Of the 177 with ulcers 17 were high grade neurotics and many were under psychiatric treatment The neurosis rates were different in the two forms of ulcer 7% for gastric and 16% for duodenal ulcer

Medical treatment was surprisingly beneficial Of 124 patients with a 5 year history and treated medically 30% required no physician visits during a 2½ year period This does not mean the patients were asymptomatic but suggests the absence of severe symptoms For 70% the physician attendances were fewer than the average for the whole practice Two thirds of the medically treated patients lost no time from work Many of the other third in addition to the ulcer had tuberculosis coronary artery disease chronic bronchitis arthritis or neurosis and the ulcer was not necessarily the prime cause for incapacity In only 25% of the 177 patients was surgery necessary Medical treatment can keep 75% of the patients comfortable

• [Statistics on the natural history of peptic ulcer are often criticized because they are based on observation of the worst cases those seen in the clinic in the hospital or by the specialist The valuable figures compiled in these London practices tend to weaken this criticism A 25% rate of operative intervention and a 33% rate of some incapacity during a 2½ year period are not too different from figures based on patients seen in the hospital or clinic —Ed]

Perforated Acute and Chronic Peptic Ulcer Conservative Treatment in 200 cases was evaluated by Hermon Taylor and R P Warren[1] (Ilford England) Of these 101 were reported previously In patients treated without operation the distinction between acute and chronic ulcer has to be based entirely on the presence or absence of a history of dyspepsia About one fourth of the perforations were of acute ulcers and a *clearcut difference has emerged between results of treatment* in the two groups Mortality complications and disability were confined almost entirely to the chronic ulcer group No patient with a perforated acute ulcer has died when treated by aspiration only one had a significant complication and nearly all have remained free from symptoms

Of 99 patients recently treated 93 had gastric aspiration with *11 deaths Seven were moribund on admission* Ten of the 11 deaths were associated with chronic ulcers and 1 was due to a perforated carcinoma Conservative treatment failed

(1) Lancet 1 397-399 Ap 14 1956

panied by food daily or at longer intervals Dumping symptoms are sometimes experienced at the same time and may be relieved by vomiting the bile

According to W Melville Capper and Richard B Welbourn[3] early postcibal symptoms if still present 1 year after surgery remain fairly constant up to 13 years thereafter In a few patients symptoms especially bilious vomiting have recurred or first developed several years after operation No correlation exists between the functional result and the age of the patient length of the history or severity of symptoms before surgery The site of the initial lesion does not affect the incidence of dumping symptoms or of bilious vomiting Patients with mild lesions (small ulcer or scar only) fared no worse than those with moderate lesions but patients with severe (large very active penetrating or stenosing) lesions showed a much lower incidence of severe dumping symptoms and bilious vomiting Women fared worse than men

The dumping symptoms or bilious vomiting are not influenced by the extent of resection in partial gastrectomy The incidence of postcibal symptoms is about the same in the various types of anastomoses The Moynihan anastomosis (antecolic afferent loop to greater curvature) has been said to cause dumping symptoms because of the afferent loop reflux which frequently follows However there is no clear connection between reflux of food and postcibal symptoms About 15% of the patients with partial gastrectomy have mild dumping symptoms but moderate and severe symptoms are twice as common after a gastrojejunal as after a gastroduodenal anastomosis Symptoms after the Billroth I procedure tend to be less persistent

Bilious vomiting is rare after the Billroth I operation but is common (1 16%) after all types of gastrojejunal anastomosis The Billroth I procedure also results in less weight loss digestion and absorption of food (especially fat) are better and colic and diarrhea are less frequent The disadvantage of the Billroth I is the higher recurrence rate when the operation is performed for duodenal ulcer

Many drugs have been used in treatment of dumping symptoms with disappointing results These include hexamethonium bromide potassium salts oral local anesthetics

(3) B t J S g 43 24 35 J ly 1955

might be achieving more favorable results than surgeons outside these centers was confirmed for this group of patients had much postoperative difficulty The incidence of the dumping syndrome within the first year was quite high—55% The major postoperative complications were weakness dumping headache and pain and 17% had recurrent hemorrhage Of the 40 patients 8 required a second operation and 2 a third 10 had severe postoperative pain 22 had the dumping syndrome 33 had weakness and only 7 had no weakness or discomfort This is a striking tabulation in a series representative of much independent surgery throughout the country

The dumping syndrome seems to follow two particular patterns (1) a syndrome of nausea vomiting and weakness occurring directly after a meal particularly one in which there is an easily absorbable carbohydrate or food to which the patient is intolerant and (2) a similar syndrome with attacks of sweating and flushing of the face developing six to eight months after gastrectomy When the syndrome develops immediately after operation slow progressive improvement occurs over 6 18 months when it develops 6 8 months after gastrectomy it is more resistant In both instances the patients respond to a dry diet of small frequent feedings with omission of easily absorbable sweets and other foods to which intolerance has developed Over 50% of the patients who had subtotal gastrectomy were unable to tolerate milk ice cream or similar products in striking contrast to the relief obtained presurgically by these measures

• [A small series—but sobering—Ed]

Early Postcibal Symptoms Following Gastrectomy Etiologic Factors Treatment and Prevention There are two main types of early postcibal syndrome each appearing while eating or a few minutes later the dumping syndrome and bilious vomiting The dumping syndrome proper—epigastric fulness distention or pressure —is accompanied by one or more of the following drowsiness fatigue and muscular weakness palpitations and sweating and a sensation of warmth Nausea colic borborygmi and diarrhea may be present but are not pathognomonic Fulness alone does not constitute the syndrome The main feature of bilious vomiting is regurgitation or frank vomiting of bile unaccom

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(3) Brit J S g 43 435 J ly 1955

sodium bicarbonate and paravertebral injection of procaine hydrochloride Temporary relief can be obtained in many patients by an injection of procaine

Surgery should be advocated only if symptoms are severe and disabling at least 18 months have elapsed since the first operation other possible causes of the symptoms have been excluded and medical measures particularly sympathetic procaine block have failed Enteroanastomosis usually relieves or greatly diminishes bilious vomiting but dumping symptoms (when also present) are relieved to a lesser extent Late results in jejunoplasty have not been good several patients have relapsed after a year or so The pantaloons anastomosis as the primary procedure has not reduced the incidence of bilious vomiting

Conversion of gastrojejunal to a gastroduodenal anastomosis has produced different results in men than in women Good functional results persisted in the men but anastomotic ulcers developed in five In women about half remained unimproved The nutritional state was sometimes improved to a remarkable degree and steatorrhea was often abolished Results were spectacular in patients who were cachectic and had a gross excess of fat in the stools

At present conversion to a Billroth I type of anastomosis is the procedure of choice for surgical treatment of all types of postgastrectomy syndrome where a gastrojejunal anastomosis is present Whatever the procedure simultaneous vagotomy would be wise to reduce the danger of recurrent ulceration

◆ [The most controversial point in this thorough review is the statement that dumping symptoms following partial gastric resection are not influenced by the extent of the resection To be sure a patient retaining three fourths of his stomach may dump and one with merely a 25% remnant may not but the trend is certainly in the opposite direction As long as a good sized gastric remnant remains gastric reservoir function is possible whereas the reservoir capacity of a tiny gastric stump is obviously limited and must be aided by adaptive mechanisms on part of the small bowel —Ed]

Alimentary Circulatory Disturbances as Cause of the So called Dumping Syndrome are reported by W Schrade and R Heinecker[4] (Univ of Frankfort) A systemic disturbance is associated with dumping Pallor coldness and moistness of the hands and extrasystoles and other changes suggesting

(4) Schw med Wchnschr 0 481-488 May 14 1955

involvement of the circulatory system are common in attacks

After patients were given a test meal of 80 100 Gm glucose pulse rate and volume and blood pressure were measured at 5 minute intervals for 30 minutes and cardiac stroke volume and output and peripheral resistance were calculated on the basis of these measurements That one patient showed a marked rise in cardiac stroke volume and output after the test meal especially when lying down was attributed to splanchnic hyperemia and regarded as an exaggeration of normal response to feeding

In three other patients cardiac stroke volume and output fell in one to 58 and 47% of fasting values in one to 51 and 24% and in one to 38 and 34% In all these changes occurred when they were sitting and lying down This is regarded as an abnormal response to feeding and attributed to loss of venous tone and dilatation of the splanchnic bed Evidence suggested that this second type of reaction might be followed by compensatory peripheral arterial constriction with subsequent recovery of cardiac output

The general subjective complaints of patients with the dumping syndrome can be attributed to the circulatory disturbances Typical symptoms of faintness dizziness and pressure in the head can be explained by cerebral anoxia but general autonomic imbalance may also contribute to the sense of malaise with an initial sympathetic overactivity followed by evidences of parasympathetic stimulation The authors believe that use of peripheral vasoconstrictors or a tight abdominal binder constitute rational treatment and report considerable success with the latter The binder does not appear to delay gastric emptying—rather the reverse

Significance of Dumping Syndrome a common and severe complication after total and not infrequently after partial gastrectomy is discussed by John M Walker Kathleen E Roberts Albert Medwid and Henry T Randall (New York) A feeling of fulness churning or discomfort in the epigastrium occurring shortly after eating or taking a hypertonic solution is succeeded by nau ea weakness sweating pallor and tachycardia lasting 60 90 minutes followed by gradual improvement and a feeling of well being until the

(5) A M A Arch Surg 71 543 550 Oct 1 1955

next meal During the acute episode patients almost invariably wish to lie down In severe cases vomiting and diarrhea may be prominent

Basic studies were made at frequent intervals after introduction of various solutions (9% NaCl 50% glucose or fructose sustagen® and starch) on six controls with intact stomachs four patients with total gastrectomies and esophagojejunal anastomoses three with total gastrectomies and esophagoduodenal anastomoses four with Ross Robertson procedures (substernal esophagojejunostomy) four with total gastrectomies and ileocecal transplants (esophagoileocoloduodenostomy) one with total gastrectomy and jejunal transplant (esophagojejunoduodenostomy) one with jejunostomy (stomach intact) and four with partial gastrectomies with gastrojejunal anastomoses

Plasma volume decreased markedly within 10 minutes after introduction of hypertonic solution reaching its maximum in about 30-40 minutes and returning to normal in 100-120 minutes Similar marked decrease in blood volume occurred with a high carbohydrate meal or a starch solution which was actually hypotonic to the plasma at time of ingestion Rapid hydrolysis of starch solutions occurred with a breakdown into many smaller molecules accounting for increased osmolarity and resultant decrease in blood volume All patients with total and two with partial gastrectomy showed decrease in plasma volume following hypertonic solution sustagen® or starch

Within 10 15 minutes after ingestion of hypertonic solution sustagen® starch or in certain patients routine hospital meals the ECG showed characteristic alterations in all patients having dumping symptoms with flattening of the T wave elevation (or occasional depression) of S T segments and occasional appearance of a U wave These changes were maximal in 30-40 minutes and returned to normal in 80 120 minutes

Both gastrectomized patients and controls showed a progressive fall in potassium and phosphate levels maximal after 90 minutes and usually still well below normal after all symptoms of dumping had disappeared When 9% NaCl was used gastrectomized patients showed clinical symptoms and signs of dumping with blood volume and ECG changes but

no alteration in potassium or phosphate levels the explanation being that when glucose is given potassium and phosphate are withdrawn from extracellular fluid and deposited with the glycogen The authors believe that depression of potassium or phosphate levels has no relation to the dumping syndrome With balloon distention with air or water up to 200 cc epigastric discomfort and nausea but no change in plasma volume hematocrit value or ECG were noted in all three patients

It seems clear that the dumping syndrome is caused by a rapid shift of circulating fluid from the blood stream into the small intestine which explains the sympathetic response with all its symptoms including the ECG changes A shock like tate due to rapid loss of extracellular fluid is produced In one patient rapid infusion of a plasma volume expander (500 cc expandex®) at time of expected dumping corrected the fluid shift and no symptoms occurred Attempts to devise an operation to insure against the dumping syndrome have not been successful

After total gastrectomy most patients lose weight Caloric intake in 15 of 20 patients was under 1 500 because they were afraid to eat By reduction of carbohydrates which are rapidly hydrolyzed to a minimum and increase of protein and fat the dumping syndrome can be controlled With use of frequent feedings about six a day and addition of protein and fat supplements caloric intake can be increased to over 2 500 calories

• [A rational explanation for the dumping syndrome is offered but the reader may entertain certain reservations Plasma volume measurements are not without their technical problems and in a previous paper (Ann Surg 140 631 1954) the same laboratory had to report the paradoxical findings of decreased plasma volume but relatively unchanged hematocrits in patients with dumping symptoms Direct measurement of fluid shifts into the intestine appear necessary to validate the hypothesis presented by Walker *et al* on the basis of indirect evidence —Ed.]

Cancer Development in Gastric Stump after Partial Gastrectomy for Ulcer Nils Helsingen and Leif Hillestad[6] (Rikshosp Oslo) followed up 303 patients who had resection for gastric or duodenal ulcer between 1919 and 1944 The ulcer was removed in every patient with gastric ulcer and in most with duodenal ulcer No signs of malignancy were found at operation Before surgery 80% of patients with gas

(6) A n S g 143 173 179 F brua y 1956

tric ulcer and 98% with duodenal ulcer had normal or high acidity

Information was obtained on 229 of the 303 patients (75 6%) All patients who died or were lost to follow up within five years of resection were excluded The analysis thus comprises 66 men and 29 women with resection for gastric ulcer and 103 men and 22 women with resection for duodenal ulcer In 11 patients cancer developed in the gastric stump an average of 30 years after operation Three fourths had had normal or increased acidity before operation Ten had resection for gastric ulcer and one for duodenal ulcer All 11 patients died The incidence of gastric cancer in the duodenal ulcer group did not differ significantly from that observed in the general population but in the gastric ulcer group the incidence was approximately three times that expected in both men and women

Patients with gastric resection for gastric ulcer have an increased risk of developing gastric cancer No evidence supports the hypothesis that the resection per se is the determining factor in development of gastric cancer

• [More kindling for the burning question When operate for gastric ulcer?—Ed]

Peptic Ulcer Partial Gastrectomy and Pulmonary Tuberculosis During recent years the belief has grown that partial gastrectomy predisposes to pulmonary tuberculosis J A Thorn V S Brookes and J A H Waterhouse[7] report a follow up study of 1¼ 6½ years of 955 patients (772 men) who had had partial gastrectomy for peptic ulcer Follow up x rays were done on 91 8% of surviving women and 90 3% of surviving men

Of the patients reviewed 809 were x rayed before operation in 60 (52 men) x ray films showed postprimary pulmonary tuberculosis i e 6 3% of those with partial gastrectomy Of seven men with positive sputum at operation tuberculosis became quiescent with treatment in four one died from tuberculosis without treatment one responded poorly and the last had positive sputum but continued to work Of 45 men whose pulmonary tuberculosis was considered inactive at least 9 subsequently had active tuberculosis within an average of 1½ years after partial gastrectomy Of eight

(7) B r M J 1 603 608 M 17 1956

women with positive x ray findings five had active tuberculosis after operation four of these did well with treatment but one died

Of 616 men and 133 women with normal x ray films before operation follow up showed 11 men with radiologic pulmonary tuberculosis Six had been under treatment and five instances were discovered during follow up Three other men in this group died from pulmonary tuberculosis since operation The annual attack rate of 5 6 for men aged 35 and over in this series after partial gastrectomy is at least five times the annual rate for pulmonary tuberculosis in the general male population of this age Eight of the 14 affected had gastric ulcer 5 had duodenal ulcer and 1 had both Annual attack rate for patients with gastric ulcer was three times that of those with duodenal ulcer (10 6 and 3 5 respectively) Patients with high gastric ulcers had the highest attack rate Of 37 men with gastric ulcer in the upper third 5 who later had pulmonary tuberculosis were among 21 who had extensive resections This group contained a larger proportion of patients who were considerably underweight before operation than did the group having less extensive resections Study of men with duodenal ulcer suggests that extent of stomach resected is not important None of the five men who had tuberculosis after operation for duodenal ulcer had had an extensive resection Patients with normal chest x rays who were less than 85% of their standard weight before operation were about 14 times more likely to have pulmonary tuberculosis than those whose weight was normal

Patients who have tuberculosis after partial gastrectomy are abnormally underweight Both leanness and ectomorphism are associated independently with increased susceptibility to pulmonary tuberculosis but low preoperative weight of patients with gastric ulcer is due mostly to undernutrition Patients already considerably below standard weight before partial gastrectomy remain so permanently afterward Development of tuberculosis after partial gastrectomy is due primarily to the presence of severe or long standing peptic ulceration with consequent undernutrition and only secondarily to effects of the operation

The authors suggest the following rules for clinical management (1) All patients should have a chest x ray before

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(7) B r M J 1 603-605 M 17 1956

clined and stabilized at an average daily output of 196-622 cc and hypersecretion could not be induced by parenteral infusions

When the accessory pancreatic duct was successfully ligated no trypsin was found in the duodenal secretion Lipase and amylase were consistently found saccharase and lactase were also present

Histamine had a slight and secretin no demonstrable effect on rate of secretion of the isolated duodenum No evidence for vagal control of duodenal secretion could be found when vagi were stimulated by insulin hypoglycemia Prolonged fasting did not depress duodenal secretion to very low levels and after the meal there was no marked secretory response There is little if any effect of feeding on duodenal secretion when food does not come in contact with the duodenal mucosa

Continued loss of duodenal secretions does not produce as severe demineralization and dehydration as occurs after loss of gastric or pancreatic juice

• [The hypersecretion and washing out effect induced in the isolated duodenal loop by parenteral infusions may have a clinical counterpart in the massive amounts of fluid often aspirated from the gut when patients with acute intestinal obstruction are given salt solutions intravenously —Ed.]

INTESTINES

Role of Golgi Complex in Fat Absorption as Studied with the Electron Microscope with Observations on Cytology of Duodenal Absorptive Cells Jules M Weiss[9] (Washington Univ) decapitated 8-10 week old male Swiss albino mice 9 minutes ½ hour 1 hour 1½ hours and 3 hours after they drank cream and removed a segment of the second centimeter of the duodenum within a minute of death In the animal killed at 9 minutes the cream was confined to the upper half of the stomach but in the others it was present in the duodenum

Under the ordinary light microscope three principal cytoplasmic organelles can be recognized in the duodenal absorptive cell the prominent Golgi complex the ergastoplasm

(9) J E per M d 10 775 82 Dec mbe 1955

partial gastrectomy (2) If partial gastrectomy is undertaken in patients with radiologic evidence of pulmonary tuberculosis the nutritional state should be improved before operation (3) If the lung lesion is active it should be treated and controlled before operation if apparently inactive close supervision is needed after operation especially for the first two years (4) Patients with a normal chest x ray film who are grossly underweight before gastrectomy should receive a high calorie high protein diet before operation

Experimental Studies on Secretions of Isolated Duodenum in dogs are reported by John H Landor Peter H Brasher and Lester R Dragstedt[8] (Univ of Chicago) who describe their technic for isolating the entire duodenum so that duodenal secretion uncontaminated with bile or pancreatic juice can be collected quantitatively

METHOD —After the pylorus was blocked the common bile duct and accessory pancreatic duct were severed The main pancreatic duct was isolated and the distal end was cut out of the duodenum along with a small button of duodenal wall surrounding it (for later pancreatojejunal anastomosis) The small bowel was severed near the duodenal jejunal junction and the proximal end was infolded after a stainless steel cannula was placed near the distal end of the duodenum Re-entry of bile and pancreatic juice into the small bowel was accomplished by (1) jejunocholecystostomy and anastomosis of the pancreatic duct to a portion of jejunum just distal to this with gastroenterostomy shortly beyond or (2) anastomosis of pancreatic duct to the ascending portion of a loop of proximal jejunum pulled into the right upper quadrant with cholecystojejunostomy done at the apex of the loop and gastroenterostomy into the descending portion of the jejunal loop

The high postoperative mortality early in the series was found to be related to potassium loss Immediately after operation some animals maintained on parenteral saline infusions secreted as much as 1 500 cc from the duodenum in 24 hours This secretion contained 5 3 9 3 mEq potassium 138 156 mEq sodium and 103 139 mEq chloride/L Thus the daily potassium loss could be as great as 14 mEq or 1 044 mg KCl Addition of 1 2 Gm KCl to the parenteral fluid prevented hypokalemia but it was also prevented in one dog by withholding parenteral fluids of all types In the early postoperative period parenteral saline thus induced a washing out of potassium and duodenal juice After the first postoperative week secretion of duodenal juice gradually de

(8) A M A Arch Surg 71 722 736 November 1955

fat absorption This complex is a system of sacs and vacuoles enclosed by smooth membranes 40 90 A thick Flattened pillow case like Golgi acs are found in compact groups just above the nucleus The lumen of each sac is narrow oppos ing walls being separated by about 90 A By dilatation of larger or smaller terminal segments the sac gives rise to the Golgi vacuoles

Study of the normal duodenal absorptive cell reveals nu merous morphologically similar osmiophilic bodies in vari ous locations Spherical and averaging 0 1μ in diameter they are found in the central lacteal in the extracellular con nective tissue space around it in the spaces between ab orptive cells within the large Golgi vacuoles and in the apical cytoplasm Their occurrence within the lacteal and their osmiophilia indicate their lipid nature

In animals deprived of food and water for 24 hours lipid droplets are scarce and the Golgi complex is greatly reduced in size consisting of only a few small sacs and a number of 400 A vacuoles in the supranuclear region (Fig 86) Thirty minutes after cream feeding the apical cytoplasm contains many vacuoles (Fig 87) Osmiophilic particles cluster at the periphery of the vacuoles otherwise electron lucent The closely packed large vacuoles in the supranuclear region can be recognized as part of the Golgi complex

During fat absorption lipid passes through the apical plasma membrane in small particles probably less than 40 A in diameter which are transformed into larger particles and deposited within vacuoles to form fat droplets The drop lets pass through the cytoplasm to the lateral plasma mem brane which they penetrate and enter the intercellular space below the terminal bar region They pass downward between the cells penetrate or pass through a gap in the basement membrane and enter the extracellular connective tissue space Finally they di sect between overlapping lay ers of the lacteal wall to enter the lacteal Although others have suggested that fat may be absorbed extracellularly it i believed that fat must pass through the apical cytopla m of the absorptive cell because fat droplets were not found in the upper part of the intercellular space

Absorption of Fats Studied in Child with Chylothorax is reported by J Fernandes J H van de Kamer and H A

When olive oil sunflower seed oil linseed oil and rapeseed oil were fed the unsaturated fatty acids contained in these oils appeared in the same proportion in chyle fat

Certain fats such as the greater part of the markedly unsaturated fats may be absorbed almost without hydrolysis Other fats must be completely or partly hydrolyzed and after resynthesis transported to the chyle Short chain fatty acids that are liberated during hydrolysis may be converted by the intestinal cells or in the liver The nature of a dietary fat therefore decides whether or not it is hydrolyzed in the process of absorption This means that the absorption mechanism is accompanied by considerable selective capacity Selection of triglycerides or fatty acids however is only possible if the fat droplets disintegrate into molecules during absorption

• [Much has been written to indicate that fats if dispersed into sufficiently small droplets can be absorbed by passing through the intestinal wall without undergoing chemical change Particle size according to Frazer should be less than 0 5μ to accomplish this Those who enthusiastically urge the administration of commercially prepared fat emulsions with the idea of promoting fat absorption in malnourished patients offer preparations with an average particle size of 1μ According to the theoretic deductions of Fernandez *et al* however if droplets of fat are to be absorbed as such, they must be broken down into particles of almost molecular size and the histologic studies of Weiss suggest that droplets of fat passing into the duodenal mucosa are no more than 40 A in diameter To make a comparison between these two sets of figures (and to evaluate the theoretical efficacy of fat emulsions prepared for oral use) th follow ing fact is necessary 1μ = 10 000 A —Ed.]

Effect of ACTH and Cortisone on Fat Absorption in Steatorrhea of Various Causes was studied by Ernst J Drenick Elizabeth Hvolboll and James A Halsted (Los Angeles) in four patients Fat balances were studied for long periods to determine whether fat absorption in steatorrhea other than in nontropical sprue could be improved by steroid therapy All stools were collected in five day pools mixed and the fat quantitatively determined Cortisone was given intramuscularly 50 250 mg daily ACTH 40 200 mg daily

A patient with steatorrhea due to subtotal gastric resection and gastrojejunostomy had no decrease in fecal fat during two periods of cortisone and five of ACTH of five days each In another patient with extensive ileojejunitis with severe malabsorption steatorrhea decreased from 50 to about 25% of daily intake In the third patient with pancreatic

(2) N w E gl d J Med 53 303 308 A g 25 1955

Weijers[1] Dietary fat was compared with chyle fat by separate quantitative determinations of all fatty acids Not all intestinal chyle accumulates in the thorax so absolute measurements of absorption via the lymph was not possible

Verzar s theory maintains that fat is completely hydrolyzed in the intestine and the fatty acids resynthesized to triglycerides in the intestinal cells via an intermediate stage of phospholipids According to Frazer s theory part of the fat is hydrolyzed into mono and diglycerides and free fatty acids in the intestine an emulsion formed and tiny droplets of neutral fat absorbed *The two theories differ essentially* in the degree of fat hydrolysis in the intestine

Chyle fat contains a mixture of intestinal and nonintestinal lymph and gives an inaccurate impression if considered entirely intestinal lymph If chyle fats are to be compared with corresponding dietary fats the admixture with nonintestinal lymph fat must be corrected The composition of the corrected chyle fat can be calculated by subtracting nonintestinal fat from total chyle fat The fatty acid pattern of corrected chyle fat can then be directly compared with that of dietary fat

Only about 10% of fat from food was recovered as chyle fat The general composition of chyle fat resembled that of dietary fat but the short chain fatty acids n tetranoic n hexanoic and n octanoic were not found in the chyle when the patient was given margarine butter or coconut oil At the same time the chyle contained long chain fatty acids the coefficient of lymphatic absorption increasing as the chain length of the fatty acid increased This difference can be explained only by hydrolysis of the dietary fat If dietary fat were absorbed without hydrolysis there would be no difference in the absorption coefficient of various saturated fatty acids

The same phenomenon was shown by feeding a synthetic mixed triglyceride This material contained 46% n octanoic acid but the chyle fat contained only 4% although the triglyceride as a whole was well absorbed Since n octanoic acid could not be found in the blood when the synthetic triglyceride was fed it was concluded that n octanoic acid does not pass the liver as such but is converted in the intestine or liver

(1) J Cl I e t 34 (pt I) 1026-1036 July 1955

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calcinosis and pancreatic insufficiency with lack of fat-splitting enzyme, fecal fat excretion fluctuated but without consistent relation to cortisone. When he was given tween* 80 neither fat nor nitrogen excretion was affected, but when pancreatic extract was administered the excretion of both decreased markedly and he was in positive nitrogen balance. The fourth patient, with severe nontropical sprue, showed definite general clinical improvement, the fecal fat being reduced from 84 to 25% of daily intake during cortisone administration.

Cortisone and ACTH may have a specific effect on the intestinal mucosa of patients with sprue and ileitis, but it seems more likely that the intestine shares in the general improvement of body tissues and that fat absorption is improved along with general restoration of normal metabolic processes in the entire body. The findings in the four patients show no direct effect on fat absorption by adrenocortical steroid.

Mechanisms Involved in Development of Vitamin B_{12} Deficiency, including deficiency of Castle's gastric intrinsic factor, bacterial or parasitic interference with absorption of vitamin B_{12}, defective absorptive capacity of intestinal mucosa and inadequate dietary intake of the vitamin, were studied by use of radioactive cobalt labeled vitamin by James A. Halsted, Marian E. Swendseid, Peter M. Lewis and Marvin Gasster[3] (Los Angeles). Absorption of vitamin B_{12} can be studied after administration of a test dose of Co^{60} B_{12} by measuring excretion of radioactivity, by measuring urinary radioactivity during 24 hours after 1,000 µg nonradioactive vitamin B_{12} is injected intramuscularly (2 hours after oral test dose) as a flushing out dose, and by surface counting over the liver (where much of the absorbed vitamin B_{12} is deposited) 6-10 days after giving the test dose.

In a normal person, regardless of dose given, apparently not much over 1.5 µg vitamin B_{12} can be absorbed. With a test dose of 0.5 µg average fecal excretion in 11 persons was 33% (range 19-57%). Patients with pernicious anemia who lack intrinsic factor secreted by the stomach do not absorb radioactive vitamin B_{12} (fecal excretion 84-100%) unless normal gastric juice is given with the test dose. In 12 patients with previous total gastrectomy almost none of the

(3) Gastroenterology 30: 1-34, J... 1956

test dose \\as absorbed unless normal human gastric juice was given also These data confirm previous evidence that secretion of intrinsic factor is limited to the stomach

Association of megaloblastic anemia with intestinal stricture or anastomosis that leaves a blind loop of intestine has been reported in 79 cases The mechanism responsible for anemia seems related to intestinal stagnation with presence of abnormal bacterial flora In three patients studied by the authors fecal excretion was high (77 98%) when $Co^{6)}$ B_1 was given alone Intrinsic factor had no effect on absorption During administration of chlortetracycline fecal excretion dropped to 33 34 and 68% respectively presumably due to decreased uptake of radioactive B_1 by bacteria Anemia from Diphyllobothrium latum is closely analogous the worm consumes vitamin B_1 present in the diet

In six patients with various intestinal disorders (regional enteritis sprue intestinal anastomosis pancreatic steatorrhea) fecal excretion of Co^{60} B_1 was 58 98% (average 74%) and neither intrinsic factor nor antibiotics influenced absorption significantly

Inadequate dietary intake of vitamin B_1 or direct deficiency is rare when a reasonably adequate food supply exists The only patient with megaloblastic anemia due to deficient diet observed by the authors had been an alcoholic for many years

Late Prognos s in Celiac Disease M K M Lindsav B E C Nordin and A P Norman[4] (London) present a survey of 37 patients studied by Hardwick in 1939 who based his diagnosis on a history in infancy of diarrhoea anorexia and loss of weight accompanied by the classical clinical features and with the finding of an excess of split fat in the stools on more than one occasion One patient had died from tuberculosis at age 17 11 could not be traced but there was no evidence that they had died Written or verbal information on seven patients indicated that four were in good health Three were under medical care two because of hypochromic anemia and one because of hypocalcemic tetany secondary to steatorrhea

The authors personally observed 18 patients (aged 17 33) 11 of whom re entered the hospital for special study Thir

(4) B r M J 1 1418 J 7 19 6

teen claimed to be in good health although four of these had insignificant digestive disturbances and four others apparently had not had a complete recovery They still had attacks of diarrhea and vomiting abdominal pain or distention and had to be careful about their diets Another regularly had two bulky stools daily Menarche in the women had tended to occur late Lack of maturity seemed characteristic only 5 of 18 were married and the only 1 of the remaining 13 who had left home had had a nervous breakdown These patients were generally underweight and somewhat undersized delicate featured and pale with immature secondary sexual characteristics Blood pressure was normal and none had clubbing of fingers

Fat absorption exceeded 90% of intake in 10 of 11 cases in 5 it exceeded 95% In 10 of 13 cases vitamin A level was under 500 units five hours after an oral test dose In four of nine patients glucose tolerance tests showed that blood sugar never rose as high as 50% above fasting level Seven of 16 patients had hemoglobin under 90% (Haldane) In five there was iron deficiency and in three (including one with steatorrhea) mean cell volume was under 80 cu μ X rays of hand and spine in 16 showed no significant abnormalities although slight osteoporosis was noted in 2 Serum calcium was within normal range in 15 of 16 cases

Superficially most of 25 adults who suffered from celiac disease in infancy seemed clinically normal 3 were under medical care for occasional relapses Only 1 of 18 personally investigated had frank steatorrhea 17 would pass any routine medical examination although 4 of these displayed indirect evidence of malabsorption indicating that recovery was not complete It is concluded that celiac disease is essentially a chronic relapsing condition The patient may be normal during prolonged periods but is liable to respond to some agent—which recently has been shown in most cases to be gluten of wheat flour—with steatorrhea

• [The evidence presented here and previously (1955 56 YEAR BOOK p 519) makes it quite clear that the intestinal defect of celiac disease persists Relapses occur not only in response to dietary factors but also to various stresses pregnancy illness or emotional trauma Inevitably the question arises whether cases of idiopathic nontropical sprue first recognized in adulthood are in fact celiac disease unrecognized in infancy —Ed]

Clinical Physiologic and Biochemical Study of Patients with Malignant Carcinoid (Argentaffinoma) is reported by Albert Sjoerdsma Herbert Weissbach and Sidnev Udenfriend[5] (Nat l Inst of Health) In five of six patients histologic proof of extensive carcinoid tumors was obtained Cutaneous vasomotor episodes and chronic diarrhea were present in all Two had a cyanotic appearance probably due to physiologic and anatomic changes in the cutaneous vascular bed Respiratory distress with a bronchospastic component was present in three as was pulmonic stenosis or tricuspid insufficiency Cardiac involvement seems to occur late in the

5 HYDROXYINDOLE COMPOUNDS IN BLOOD AND URINE

S J	B S (µ /M)	U 5 HIAA (MG / 4 H)	T U 5 OH I d l (M / 4 H)
Normal	0 1 0 3	2 9	†
Ca cinoid			
1	2 5	320 392	453
2	0 5 1 5	240 280	345 385
3	1 2 1 9	380 590	460 865
4	1 7 2 7	214 572	336 640
5		140	
6		76	

R g f l bout 40 on oid p
†M m t t f bl on m l b f la g d l t on q d t
l mi t t f g b t

course One patient had diarrhea and flushes without demonstrable liver metastases Hypotension during flushes was marked in two patients Four had arthritic symptoms Azotemia during flushing with profound diuresis on ces ation of the episode in one patient suggested action of an antidiuretic mechanism during the flush consistent with the effects of serotonin on the kidney

Blood levels of serotonin were greatly elevated (table) and all the circulating serotonin was found in the platelets None could be detected in cerebrospinal fluid Urinary excretion in carcinoid patients was 1 2 mg /day (normal under 0 1 mg) Excretion of 5 hydroxyindoleacetic acid (5 HIAA) a metabolite of serotonin in urine was many times normal and other 5 hydroxyindole compounds were found in appreciable quantities Because of extreme elevation of urinary 5 HIAA its measurement provides a simple and rapid diagnosis of malignant carcinoid

(5) Am J M d 20 5 0 53 Ap 1 1956

Studies on experimental animals showing serotonin to be derived from the amino acid tryptophan suggested that there might be an abnormality of tryptophan metabolism in this condition Steps in the 5 HIAA pathway of tryptophan metabolism are shown in Figure 88 In dogs and normal human volunteers urinary excretion of 5 hydroxyindoles is relatively constant over wide ranges of tryptophan intake amounting to about 1% In marked contrast excretion of these substances by carcinoid patients varies with amount of tryptophan in the diet on a daily intake of 500 mg (2 45 mM) as much as 60% of dietary tryptophan was converted to 5 hydroxyindoles Probably more 5 hydroxyindole compounds are formed than are excreted in urine as serotonin given to normal subjects is recovered only to about 80% as 5 HIAA in urine These experiments establishing tryptophan as the dietary precursor of serotonin and its metabolites in man were confirmed with isotopically labeled tryptophan

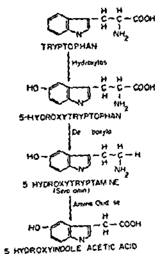


Fig 88 —The 5 hyd xyi dole p thway of t yptophan m tabol m (Courtesy of Sjoerdsma, A. et al Am J Med 20 520 532 April, 1956)

In the carcinoid syndrome up to 60% of dietary tryptophan may be diverted by the tumor to the serotonin pathway leaving less of the amino acid available for formation of niacin and protein Hence symptoms attributable to excess serotonin and to niacin and protein deficiency are to be expected Bronchoconstriction diarrhea and vasomotor disturbances in the carcinoid syndrome are attributable to serotonin and have been reproduced experimentally Although pellagra has been reported the authors patients showed no signs of niacin deficiency except diarrhea however they all received vitamin supplements including niacin

Brunner Type Glands in Regional Enteritis C A Kawel Jr and Henry Tesluk[8] (Henry Ford Hosp) examined vary

(8) G stroent l gy 28 810 8 0 May 1955

ing lengths of ileum resected from 34 patients with regional enteritis The morphologies of the aberrant glands could be recognized by routine staining but were further differentiated by indulin mucicarmine stains Brunner gland cells stain red with mucicarmine and intestinal mucous secretions stain black with indulin

In the ileum of 16 patients Brunner type glands were found (Fig 89) The glands resembled the Brunner glands in

Fg 89—M osa f leum h wı g la g mbe of Bru type gl d se of g on l ent t Hen t xyl -e ın d d f m ×7) (Court y f Kaw l, C. A J d T l k H G t oent logy 28 810 8 0 M y 1955)

the duodenum and pylorus of the stomach They begin abruptly and no transitions with intestinal glands are seen Changes of this type were not encountered in bowel resected in other chronic inflammatory diseases except in one case of tuberculous enteritis

No relation could be established between microscopic findings age of patient duration of symptoms severity of illness or length of bowel involved or resected However all 16 patients had been operated on previously because of their disease and in two thirds symptoms recurred None of the 18 patients without Brunner type glands had recurrences

Possible explanations for the development or occurrence of these peculiar glands must include both heterotopia and metaplasia Indulin stain studies indicate that the secretion of these glands is chemically different from that of the intestinal mucosa This change is not merely morphologic but represents a change in function

There is no evidence that such changes occur before onset of regional enteritis It is much more likely that they follow its development The presence of such changes should make later recurrence more probable

Syndrome of Combined Ileocolitis refers to granulomatous ileitis and nonspecific ulcerative colitis two distinct pathologic processes in the same patient Rappaport and co workers reported 100 cases of regional ileitis in 55 of which the granulomatous process extended into the colon In many cases it could be detected only microscopically In the experience of Harry Yarnis[7] (New York) granuloma of the colon secondary to ileitis is rare and usually due to fistulous tracts originating in the diseased ileum

Of 654 patients with ileitis 1 520 with universal ulcerative colitis and 109 with segmental colitis seen during 25 years only 54 had combined ileocolitis In 38 both diseases were present when the patient was first seen In 12 the terminal ileum was involved first and ulcerative colitis developed after the ileum was connected to the transverse colon Four had ulcerative colitis of the entire proximal colon originally followed by granulomatous ileitis within two to five years after subtotal colectomy and ileosigmoidostomy Of the 38 patients with combined ileocolitis when first seen the terminal ileum and ascending colon were involved in 16 terminal ileum and transverse colon in 2 terminal ileum and distal colon in 5 terminal ileum and entire colon to the sigmoid in 10 and ileum jejunum and entire colon in 5

Although ileitis and nonspecific colitis present different pathologic features they seem related Age distribution is the same and symptoms are similar Symptoms of combined ileocolitis are similar to those of both diseases but more severe beginning most often during the second decade Temperature usually ranges between 101 and 102 F Cramps and bloody diarrhea almost always occur anorexia and weight

(7) J Mt S H p 2 159 169 1955

loss are marked during recurrences Intestinal obstruction abdominal distention and fluid levels in the small bowel respond to intestinal intubation Three patients had constipation 7 massive hemorrhage 2 melena 14 arthritis 5 duodenal ulcer 4 erythema nodosum 2 stomatitis with ulcerative pharyngitis 2 phlyctenular conjunctivitis and 20 perirectal abscesses and fistulas Four patients had internal and six external fistulas originating in diseased bowel

Insoluble sulfonamides and antibiotics are helpful in treating infection penicillin is of no value Steroid therapy is most effective as ACTH parenterally Cortisone hydrocortisone and prednisone orally are disappointing because of uncertain absorption Extensive resections of the colon and small intestine were necessary in several patients because of massive hemorrhage or progression of the disease Local palliative resections of stenosing granulomatous areas in the small intestine are frequently necessary due to obstruction even though the disease is diffuse Of 11 patients with diseases limited to the terminal ileum and ascending colon 8 had ileocolic resection and 3 a short circuiting procedure Results were good in four six had recurrences and one died after a secondary resection

Prognosis is poor in this syndrome Of 16 patients treated medically 3 are well 4 improved and 7 in poor condition 2 were lost to follow up Of 38 treated surgically 9 had good results 6 improved 18 are in poor condition 2 are dead and 3 are lost to follow up 11 eventually required ileostomy Conservative treatment should be tried if there are no urgent surgical indications (massive hemorrhage intestinal obstruction or persistent fistulas)

• [What do s it s gnify in terms of pathogenesis that ulce at ve colitis followed ileotransver e colostomy for ileitis n 12 cases and that ileit s followed an ileosigmoidostomy for ulcerat ve colitis in 4? As everyone knows since the events of June 1956 in Washington the medical p o fession doesn t know beans about ileitis —Ed]

Acute or Subacute Ileitis was studied radiologically in 70 children by E Cherigie C Tavernier J Dupas and Raynal [8] Some were convalescents others were in the eruptive stage of measles or scarlatina and some had mild ore throat or mumps A few were examined after surgery which had disclosed mesenteric lymphadenitis In certain patients serial

(8) J d l t él ct 1 36 796 798 1955

radiologic studies of the ileocecal region were made with the purpose of ascertaining whether the terminal ileum was normal or pathologic Frequency of localized changes in the terminal ileum is related to the large amount of lymphoid tissue in this segment which reacts like a true tonsil to the most diverse stimuli hence it is the principal site of mo tor ganic affections of the small intestines and also of the intes tinal phase of generalized infectious diseases

Contrary to results cited by others the authors believe that in the infant the radiologic appearance of the lymph follicles is not constant in the terminal ileal loop In the healthy infant examination shows a segment 2 3 cm in dia meter supple and mobile Compression causes a longitudinal crease variable and inconstant Anomalies of muco al pat tern indicate development of the lymphoid system In infan cy the ileal segment appears dilated and the follicular pat tern is more definite and larger similar to that in nonscleros ing ileitis Follicular patterns are affected by peristalsis and may disappear with passage of a contractile wave

In typhoid fever lymphoid follicles and hypertrophied Peyer s patches were demonstrated Early tuberculosis of the small intestine is characterized by hyperplasia of lymphoid tissue in the ileocecal region At first clear oval shadows are noted in the terminal segment arranged lengthwise and consisting of juxtaposed lymphoid masses Later these islets expand and form large marginal lacunar defects a few centi meters from the valve This is an extremely hypertrophied Peyer s patch Later lymphoid hyperplasia extends to the whole cecum which has a characteristic studded appearance Intestinal borders become irregular because of ulceration

Like acute *lymphadenitis in the child* the clinical manifes tations of Crohn s disease generally begin with a pseudoap pendical syndrome Pathologically the disease consists of hypertrophy of Peyer s patches with significant lymph node hyperplasia The lesions are segmented At outset radiologic differentiation from tuberculosis or acute primary lym phadenitis is impossible but later progression yields a char acteristic picture

The authors reach the following conclusions (1) Lym phoid hypertrophy of the terminal ileum is a pathologic man ifestation in the child Possibly in certain patients the folli

cles may appear spontaneously but these most often reflect localized lymphoid accumulations Extension of the process to the entire terminal segment is abnormal (2) Hyperplasia localized in the ileocecal region may be secondary to an infection that causes generalized lymphatic hyperplasia This type of lymphadenitis accompanies measles scarlatina anginas pneumonia and mumps It explains the appendical symptoms that often precede by 24 hours the onset of an infectious disease Less frequently it may be a primary disorder of viral etiology (3) Primary mesenteric lymphadenitis and follicular ileitis seem to be the same disease Lymphatic hypertrophy is always present and appears more marked in the adult (4) As differentiation from early Crohn s disease is practically impossible numerous cured cases of Crohn s disease may be mild inflammatory lymphoid ileitis (5) Mesenteric lymphadenitis usually simulates appendicitis making decisions regarding surgical treatment difficult During an epidemic of sore throat measles or grippe radiologic examination may reveal ileal signs and unnecessary operations for epidemic pseudoappendicitis may thus be avoided

• [Unfortunately the authors do not provide pictures of the x ray findings In normal infants honeycomb appearance of the terminal ileum, caused by prominent lymphoid follicles is apparently not unusual In older children and adults the same x ray pattern—Golden called it nonsclerosing ileitis —may represent a hyperplastic lymphoid reaction to a transient infection or irritant. The important point is that unusual x ray patterns in the small and al o large bowel do not necessarily mean serious d sease especially if the patient is under 16 Failure to appreciate this has led to rather extensive resections of the ileum or colon for no more than benign lymphoid hyperplasia —Ed]

Recognition and Present Treatment of Endemic Fish Tapeworm Infestation (Diphyllobothriasis) Julius Rosenberg Edith Neumann and Milton J Matzner[9] (Jewish Hosp of Brooklyn) report 13 cases diagnosed at the hospital between 1950 and 1953 All patients were Jewish females who had tasted partially cooked gefullte fish during its preparation The youngest a student nurse aged 19 had tasted it as a child while the grandmother was cooking the fish

The physician was consulted by 12 of the patients because segments of the worm were passed 9 brought the segments with them The others had the ova of D latum in the stools This tapeworm can be differentiated from the meat tape

(9) Am. J G troenter 1, 24 121 136 A gu t, 1955

worms Taenia solium and T saginata because the proglottids are much broader than they are long and only the oldest farthest from the head are approximately square The proglottids of T saginata and T solium are either square or the length is greater than the width Only six patients had gastrointestinal symptoms of these one also had amebiasis another duodenal ulcer and a third a poorly functioning gall bladder and two duodenal diverticula Complete blood counts in 11 revealed no anemia or eosinophilia One patient had anorexia weakness and weight loss probably of psychogenic origin

All fresh water fish should be thoroughly cooked before ingestion Heating at 65 C for 5 minutes kills the larvae of D latum in ordinary cooking fish is subjected to 100 C or more for at least 10 minutes Cooks should be warned not even to taste raw or partly cooked fish or its soup even if they do not swallow it

Treatment of choice is atabrine® orally or by duodenal tube for a total of 0 6 1 Gm The important side effects nausea and vomiting may be minimized by duodenal administration Severe side effects appear in only a few of the millions taking the drug and only after prolonged use which is not necessary when it is used as an anthelmintic Atabrine® must be carefully administered to children

Pathogenesis and Treatment of Acquired Megacolon Arrigo Raia[1] (São Paulo) presents the findings in 205 adults with megacolon In Brazil megacolon is the most frequently occurring surgical disease of the rectum and sigmoid more common than carcinoma

Megacolon is of two types congenital and acquired The congenital type seen in the newborn or during the first years of life is caused by agenesis of the myenteric plexuses of the terminal colon It is common in the United States but seldom seen in Brazil In acquired megacolon chiefly in adults the myenteric plexuses of the colon normal at birth are destroyed by an unknown agent

Grossly a segment of colon usually the sigmoid colon is noticeably dilated and elongated and occupies a great part of the abdominal cavity pushing the viscera upward and to the right The walls of the rectum and sigmoid are thick and

(1) S g Gy ec & Ob t 101 69 79 J ly 1955

the muscular layers hypertrophied There is no evidence for achalasia of the pelvirectal sphincter as the sole cause of megacolon

Microscopically the myenteric plexuses were most deranged in the distal rectum for a distance of 10 20 cm beginning in the internal sphincter of the anus No nerve cells could be seen in most sections from this segment Above this in the most advanced cases severe plexus lesions were found but less acute than those in the segment just above the sphincter The pathologic condition was less evident in sections from the cecum and ascending and transverse colon

Acquired megacolon is a progressive disease not only of the colon but of the whole organism The severity varies along the entire colon and is most pronounced in the terminal rectum

Whether the causes of congenital and acquired megacolon are the same is unknown In none of the adult cases examined was there evidence of congenital megacolon

When the myenteric plexuses of an intestinal segment are diseased functional harmony is destroyed Peristaltic waves to this segment are disrupted and continuity is lost as if the plexuses did not exist This segment of bowel contracts because it is hypertrophic but the contractions are not synchronous with peristaltic movements and sphincter actions Evacuation is impossible and fecal stasis results

Of 205 patients 41 were treated with sphincterectomy and 90 with rectosigmoidectomy None of the patients who had sphincterectomy were benefited Failure was probably due to three circumstances (1) The lesions involve more than one segment and resection of one does not remove the entire obstacle to fecal transit (2) The borders of the intestinal muscles may reunite through scar tissue and the same conditions become re established (3) Sphincterectomy removes only a band of muscle of the rectum and sigmoid while the plexus lesions in the rest of the segment remain to impede evacuation

The most satisfactory results were obtained in two or three stage rectosigmoidectomies by Swenson s pull through technic The mortality was low and complications due to the operation were mild especially if a transverse colostomy was used to reduce the likelihood of disruption of the suture line

Studies of Ulcerative Colitis III Nature of Psychologic Processes George L Engel (Univ of Rochester) analyzed 39 patients and reviewed the psychologic data given on 41 others for any consistent patterns as a whole or relative to exacerbations and remissions No assumption is made that such correlations have etiologic significance or that the cause of ulcerative colitis is psychogenic

Many patients are described as having obsessive compulsive character traits some as being petulant querulous demanding and provocative but with well directed aggressive actions all have been described as immature referring to their dependency intolerance to frustration and restricted relationship with people These traits are not specific for ulcerative colitis Most people with such traits do not have this disease but most patients with ulcerative colitis do have these major character traits

Patients with ulcerative colitis may have a dependent relationship with one or two persons but cannot establish warm genuine friendships with others The patient seems to live through and depend on the key figure (i e mother) and refrains from initiative or from planning independent action Any interruption of doctor patient contact especially early in the relationship is likely to cause symptomatic relapse Among 10 patients 24 of 30 relapses involved real threatened or symbolic separations During 45 onsets and relapses in 16 patients the feeling tone was expressed as helpless overwhelmed and too much to expect of me

Most of the mothers appear dominating and often exert control by assuming the role of a martyr Most of the information about the mothers comes from the patients The consistent description may reflect the common psychology of the patients with ulcerative colitis or may indicate a close similarity among the mothers Probably both factors contribute In patients with ulcerative colitis sexual development is inadequate

The most frequent initial symptom is bloody stool often preceding diarrhea Many patients had rectal bleeding or abrupt severe constipation for days weeks or months before diarrhea began The most common alternative symptom in 20 of 23 patients whose histories were carefully taken was headache

(2) Am J M d 19 231 256 A gust 1955

Ulcerative colitis involves particularly the lining surface of the bowel and possibly the functions necessary to maintain an effective and selective barrier against penetration into the organism including psychologic and behavioral aspects Why is the colon the affected site? Bowel dysfunction usually constipation long antedates the colitis but this is not evidence for a primary defect in the bowel wall If such defects exist developmental or acquired early in infancy they may contribute to localization of the disorder in the bowel as well as to total personality development

Despite the general impression that psychosomatic and psychotic manifestations are mutually exclusive this has not been demonstrated in ulcerative colitis Five patients have shown psychotic behavior and active colitis at the same time

In this formulation ulcerative colitis develops in certain individuals under specific circumstances only when other adaptive processes fail and the significant object relationship is threatened or actually interrupted So long as the relationship is maintained other pathologic processes may become manifest but not colitis Pathologic character traits maintain the key relationship and satisfy needs within that framework

When separation is not or cannot be dealt with by psychologic mechanisms physiologic changes are initiated which interfere with or disrupt other adaptive or integrative processes permitting tissue breakdown disturbed local tissue growth invasion by viruses or bacteria etc The nature of the tissue process although associated with the separation reaction is unknown nonspecific and without primary psychologic meaning

• [A happy event to have a psychiatrist—or any physician for that matter—approach the problem of ulcerative colitis not sweepingly but cautiously! As Engel points out many formulations based on the symbolism of diarrhea ignore the fact that patients with ulcerative colitis may actually be constipated either initially or at various times during their illness their rectal discharges are purulent and bloody but the stools at such times are hard and infrequent The validity of various investigative procedures designed to relate bowel function to emotional states is also questioned. Since an intimate doctor patient relationship is fundamental in the therapy of the disease what is the significance of studies in which the patient submits to stress interviews and painful procedures in a desperate effort to maintain his doctor's good will?—Ed.]

Ulcerative Colitis and Pregnancy Burrill B Crohn Harry Yarnis Edward B Crohn Robert I Walter and Lester J Gabrilove[3] (Mount Sinai Hosp New York) analyzed the

(3) G t oent logy 30 391-403 M h 1956

effect of 150 pregnancies in 110 women aged 17 46 years with ulcerative colitis They were classified as group I previous colitis quiescent at onset of pregnancy group II colitis active at inception of pregnancy group III onset during pregnancy and group IV onset post partum

The 47 women in group I had 74 pregnancies Colitis was adversely affected during the pregnancy or became active during the puerperium in 40 pregnancies (54%) Only 32 women had a normal pregnancy without flare up Most recurrences appeared in the first trimester and next most commonly post partum In the 25 women in group II (38 pregnancies) pregnancy aggravated the disease in 29 pregnancies (75 3%) chiefly in the first trimester and then post partum The course is not predictable on the basis of the severity of the colitis at time of conception Recurrence or exacerbation rates of 55 5% in group I and 76 3% in group II are high it seems that if pregnancy had not occurred the recurrence rate would have been lower

In group III (19 pregnancies) the colitis appeared *de novo* during pregnancy most often in the first trimester In group IV (19 pregnancies) ulcerative colitis began post partum after an uneventful pregnancy and delivery

Apparently fertility is not affected Many women had several pregnancies before the onset of colitis (43 births) and many had several pregnancies after the disease was recognized Since the patient s life is rarely threatened and assuming that the pregnancy is desired the disease should be treated symptomatically and the pregnancy carried through Chances of delivering a viable infant are as good as in the general population Transfusions are often necessary and the free use of antibiotics is not contraindicated ACTH the most effective drug for ulcerative colitis is not deleterious to pregnancy if given intramuscularly

In group I pregnancy should not be interrupted In group II the high incidence of exacerbation of colitis during the first trimester may indicate abortion If the baby is highly desired the threat of the disease can be balanced against the fulfilment of this desire but if pregnancy is unwelcome or the mother emotionally disturbed and psychologically immature the physician may decide to interrupt the pregnancy In group III abortion becomes urgent if coli[illegible] s in

the early months of pregnancy and is severe since the disease can be fatal Subsidence of symptoms usually follows abortion

The patients should be delivered by usual methods Cesarean section is not indicated Those who have had corrective major surgery such as permanent ileostomy and colectomy tolerate pregnancy uneventfully

Cortisone in Ulcerative Colitis Final Report on a Therapeutic Trial is made by S C Truelove and L J Witts[4] (Oxford) Cortisone was given to 109 and a placebo to 101 patients with typical chronic ulcerative colitis The dosage in most patients was 100 mg daily for six weeks or 100 mg daily for two or three weeks followed by 50 75 mg daily for the next three to four weeks

After six weeks treatment two of five patients taking cortisone were in clinical remission compared with less than one of six on placebo therapy Cortisone was particularly effective in first attacks Regardless of initial severity in first attacks and relapses the cortisone treated group was more improved than the control group

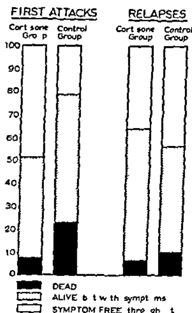
Clinical and sigmoidoscopic findings correlated satisfactorily after six weeks of treatment However some patients in clinical remission showed no sigmoidoscopic improvement whether or not cortisone had been given Some clinicians have claimed that cortisone may suppress symptoms of ulcerative colitis while the disease remains active This apparently occurs in some patients even though cortisone has not been given

Bowel perforation general peritonitis and death occurred in two patients both in the control group In this series therefore cortisone did not predispose to perforations Except for possible pyogenic and eye complications the cortisone treated patients were no more prone to complications than the controls Perhaps antibiotics combined with cortisone may further reduce the risk of complications

Of the total 210 patients adequate follow up from nine months to two years was obtained in 205 Nine months after the trial period patients who were treated with cortisone during their first attack maintained a clearcut advantage over comparable controls The initial advantage of cortisone ther

(4) B t M J 1041 1048 O 9 1955

apy in patients treated for a relapse was lost during this pe riod (Fig 90) As the follow up continued beyond nine months the number of deaths increased slightly and the number of asymptomatic patients decreased Patients treated with cortisone for a first attack still maintained an advantage over patients whose first attack was untreated Patients in



F g 90—St te of pat ent e m nths afte t i l p od (Co rt sy of Tru love, S C nd W tts L. J Brit. M J 2 1041 1048 Oct 9 1955)

relapse at the time of therapy had no long term advantage over corresponding control patients

Total deaths were 25 (11 9%) Sixteen died during the six weeks trial period—5 among the cortisone treated and 11 of the controls Ileostomy with or without colectomy was per formed in 44 patients and 14 died Of the 14 deaths 8 occurred during the trial period—2 in the cortisone treated and 6 in the placebo group Of the total patients 119 had symptoms and 61 w e asymptomatic at follow up

Patients with early ulcerative colitis should receive corti sone promptly in doses sufficient to suppress the disease

Treatment should promptly be resumed if symptoms recur Resolute medical treatment for the first few weeks supplemented by cortisone and followed by careful supervision may prevent irremediable damage to the colon

Influence of Hormonal Therapy for Ulcerative Colitis on Course of Surgical Treatment Mark A Hayes and Samuel D Kushlan[5] (Yale Univ) reviewed the findings in 24 patients with active chronic ulcerative colitis Twelve had received or were receiving steroid therapy Of the 24 patients 13 had surgery of 7 receiving steroids 1 died and 1 of 6 not on steroids died

Of the 12 patients receiving adrenocortical steroids 8 had some serious complication during observation Three patients who had one stage ileostomy and subtotal colectomy had severe exacerbation in the retained large bowel segment as steroids were gradually withdrawn postoperatively One of these required an emergency abdominal perineal resection of the rectum for bleeding and small bowel dysfunction Bacteremia developed in two patients while on cortisone One case was fatal due to hemolytic Staphylococcus aureus resistant to all antibiotics and one was manifest as multiple metastatic abscesses Two patients had clinically unrecognized perforation of the colon while taking steroids and one died In one patient status epilepticus developed while adrenocortical function was being maintained postoperatively at a high level by ACTH therapy Intractable shock refractory to adequate blood replacement due to relative adrenocortical insufficiency accounted for a third of the complications and occurred in 5 cases 2 6 8 11 and 24 months after hormone therapy had been discontinued

The total dosage duration of therapy and time free from steroids are not reliable indexes for judging pituitary adrenocortical responsiveness and chances for surviving an operative procedure If the patient is taking cortisone additional intramuscular depots of cortisone may be given before surgery but the patient is more easily controlled if changed to daily intravenous infusions of ACTH using eosinophil counts as a guide If the patient is on ACTH therapy intravenous infusion of ACTH is given throughout the operation If the patient has been taking steroids but this was unknown

(5) Gastroenterology 30 75-84 January 1956

before surgery readily soluble forms of hydrocortisone can be given intravenously during surgery Dosage is determined by clinical response

• [When surgery is contemplated for patients who are receiving adreno cortical therapy for ulcerative colitis the main problem is not as was first feared poor wound healing but as emphasized here maintenance of adequate pituitary adrenal function and control of sepsis —Ed]

Mucosal Grafted Ileostomy in Surgical Treatment of Ulcerative Colitis According to Rupert B Turnbull Jr and George Crile Jr [6] (Cleveland Clinic) ileostomy dysfunction

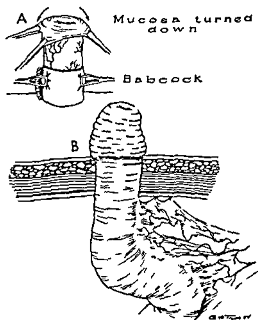


Fig 91 —M l g afted l t my A f mat B mpl t n (C tesy f T rnbull R B J a d C il G J J A M A 158 32 34 May 7 1955)

(obstruction) constitutes the primary postoperative hazard now that the incidence of fatal postoperative peritonitis has decreased The construction of the conventional ileostomy violates a fundamental surgical principle the vulnerable serosa of the ileostomy is left exposed To prevent the inflammation and functional obstruction that often follow this type of

(6) J A M A 158 3 34 M y 7 1955

ileostomy the authors have developed the mucosal grafted ileostomy (Fig 91)

TECHNIC.—This depends on removal of serosa and muscle from the terminal inch of the ileostomy At least 2 in of ileum is pulled through the abdominal wall and its terminal inch demuscularized This is carried out by making circumferential and longitudinal incisions through the seromuscular layers and developing a cleavage plane between the circular muscle and the submucosa The seromuscular layers then strip off easily unless chronic serositis has been present The resultant mucosa submucosal tube which is viable because blood vessels are carried primarily in the submucosa is then everted turned down over the ileostomy and sutured to the skin edge around the base of the ileostomy The ileostomy is not dilated and tubes are not inserted Some traumatic edema may be present for three or four days but no inflammatory changes are found

Colectomy and mucosal grafted ileostomy were performed in 21 patients Parenteral fluid therapy was required in five after the nasogastric tube was removed—because of acute postoperative enteritis in three peritonitis due to preoperative perforation of the colon in one and large fluid losses through retroperitoneal lymphorrhea in one No patient had abdominal cramps No reconstruction of an ileostomy was required up to 19 months postoperatively and no enterocutaneous fistulas developed Ileostomy obstruction was notably absent Ileostomy diarrhea was not observed except temporarily in the three patients with acute postoperative micrococcic enteritis

• [Through the kindness of Dr Turnbull a follow up report as of April 1956 is available In 50 patients undergoing subtotal colectomy with mucosal grafted ileostomy in one stage 1 died from staphylococcic enteritis after the operation and another had to have laparotomy with reconstruction of the ileostomy due to retraction about a year later Forty nine patients are completely rehabilitated The only additional operative procedures carried out on these have been excision of skin strictures in three as outpatients one graft sloughed completely leaving the patient with a conventional ileostomy

If the internist can be reassured that ileostomy dysfunction will develop in no more than 10% of cases he will be even more ready to turn to the surgeon for the management of ulcerative colitis —Ed]

Experiences with Prefrontal Lobotomy for Intractable Ulcerative Colitis Preliminary Report Richard W Levy Harry Wilkins Jess D Herrmann Achilles C Lisle Jr and Alvin Rix[7] (Univ of Oklahoma) report five patients with ulcerative colitis unresponsive to medical and psychiatric treatment in whom colectomy was contraindicated Each

(7) J A M A 160 1 77 1280 Ap 14 1956

had varying degrees of obsessive compulsive behavior deep-seated hostility and periods of depression

Three patients had complete remission of colitis after prefrontal lobotomy One patient died of complicating intestinal obstruction Another did poorly stools increased to eight daily and colectomy was done but the patient died of septicemia

There are two possible explanations for the beneficial effect of prefrontal lobotomy in these patients Alteration of the patient s personality may occur so he no longer expresses his emotions through his colon or the lobotomy incision may actually sever autonomic association fibers between the cerebral cortex and hypothalamus There is ample evidence that the premotor area orbital surface of the frontal lobe and cingulate gyrus project on the hypothalamus and serve as autonomic regulators The hypothalamus is known to control the paraspinal sympathetic ganglions vagus nerves and sacral plexus

Candidates for this procedure must have had persistent bloody diarrhea for months despite intensive medical management Additional factors are excessive weight loss (more than 25% of normal) and psychiatric symptoms refractory to therapy

CASE 1—Woman 43 had 25 bloody stools daily and her weight was 106 lb Barium enema revealed a tubular rigid colon with shortening and loss of haustration After prefrontal lobotomy colitis became and remained quiescent Barium enema revealed lengthening of the intestine increased pliability and moderate return of haustrations She has done well for over five years

CASE 3—Woman 32 had had intermittent attacks of ulcerative colitis for 10 years Before lobotomy she had 24 stools daily Her weight was 85 lbs Within two weeks of lobotomy weight gain began and the stools gradually decreased to four a day One year later she had one stool daily and had become pregnant

• [Readers of last year s YEAR BOOK may recall that two French physicians undertook to heal peptic ulcer by injecting procaine into the frontal lobes More vigorous manipulation of man s noblest organ appears to be in store for those with severe ulcerative colitis—at least for the patient who prefers to part with his finer sensibilities than with his colon Unless surgeons perfect a technic for soulectomy they seem to have gone about as far as they can go in seeking to attack the very ultimate organ responsible for ulcerative colitis The fact perhaps that frontal lobe responsibility is assumed rather than established (even the anatomic pathways between cerebral cortex and colon are uncertain!) might give pause to some Furthermore in evaluating the results in the five patients treated by lobotomy it must be recalled that the one predictable feature of ul

cerative colitis is its unpredictable response to treatment soothing kindness may induce a remission but so may gross insult whether artificially induced fever or surgical trauma —Ed]

Diverticulitis Progress toward Wider Application of Single Stage Resection was reviewed by Edward S Judd Jr and Thomas W Mears[8] (Mayo Clinic and Found) Of 329 patients who had surgery for diverticulitis 68 were treated by single stage resection and primary end to end anastomosis

Of these 68 patients 21 had palpable masses and 13 had masses detected by digital examination of the rectum Signs and symptoms of obstruction in the sigmoid colon were present in 20 Six had severe bleeding and no cause other than diverticulitis could be demonstrated In none was hemorrhage the only indication for surgery Fistulas were present in 15 patients

Only 1 of the 68 patients died postoperatively from a condition unrelated to resection and the average hospital stay for the others was 17 days The low morbidity and mortality *in this type of surgery suggests that prophylactic resection* can be offered certain patients with uncomplicated diverticulitis

Three groups of patients may be candidates for elective prophylactic single stage resection The first group has recurring attacks of diverticulitis despite good medical care The more attacks a patient has the more likely is he to develop serious complications The second group consists of patients who have urinary symptoms with an attack of diverticulitis These symptoms indicate that the urinary bladder is threatened by the inflamed sigmoid colon In the third group are patients in whom cancer cannot be excluded preoperatively In 22% of patients who had x rays with barium enemas the exact nature of the lesion could not be determined

Resection must not be undertaken during an acute attack Only after the inflammation has subsided should prophylactic one stage resection be considered

• [Unfortunately our astounding ignorance concerning the natural history of d erticulitis compromises sound decis on in deciding whether a patient who has had one or more bouts of diverticulitis should have interval surgery Figures are simply not available and the authors have to but

(8) A M A Arch. S rg 70 818 825 J 1955

tress their assertion that repeated attacks of diverticulitis increase the likelihood of complication by the statement *it seems obvious*

In a discussion on the surgical treatment of diverticulitis Snapper (Am J Gastroenterol 24 400 1955) draws attention to a relatively un known complication Diverticulitis is also oftentimes the cause of *fever of unknown origin* *Occasionally communications exist between* a small branch of the inferior mesenteric vein and one or more diverticula Every time this communication breaks open chills and fever develop The blood culture is always negative because the bacteria are filtered off by the liver —Ed]

Ameboma of Intestine Analysis of Disease as Presented in 78 Collected and 41 Previously Unreported Cases The cri terion for selection of cases by Ryle A Radke[9] (Fitzsimons Army Hosp) was a localized tumor like lesion in patients from whom Endamoeba histolytica was isolated or in whom the reaction to the complement fixation test for amebiasis was positive Ameboma (amebic granuloma) is a localized thickening of the intestinal wall around an ulceration caused by E histolytica often mistaken for neoplasm because of the narrowed intestinal lumen or the presence of a palpable mass

The ameboma was located *in the rectum in 48* cecum in 43 transverse colon in 18 sigmoid colon in 11 ascending colon in 11 descending colon in 6 and in various sites in 15 *A mass first appeared in 12 patients during antiamebic ther apy* The most common physical finding was an abdominal or rectal mass (77 cases)

X ray findings were most often interpreted as malignancy even in one patient who had three filling defects Barium en ema examinations often revealed serrations before treatment Stools were positive for ameba in 59 patients and negative in 12 results were unknown in 47 Results of sigmoidoscopic examination were positive in 43 patients negative in 9 and unknown in the remainder Biopsy tissue contained ameba in 27 cases but was negative in 18

Of the 119 patients 41 died only 8 of whom had received antiamebic therapy Operations were performed in 52 of whom 26 died (out of 42 with adequate follow up) Two pa tients who collapsed and died after rectal biopsy were found to have edema and/or hemorrhage of the adrenal cortex (Waterhouse Friderichsen syndrome)

In the 52 treated patients emetine alone (in 15) or in com bination (in 20) was the agent most often used In 11 pro

(9) A I t M d 43 1048 1066 N mbe 1955

longed therapy was necessary and in 5 the stools remained positive for E histolytica despite massive doses of emetine and clinical improvement

Patients had intermittent diarrhea often bloody lower abdominal cramps low grade fever malaise and weight loss Thirty one had intestinal obstruction either intermittent or complete in 6 this occurred during antiamebic therapy Amebiasis cutis as a complication of surgery or perianally was unusual The skin involvement was associated with severe pain and excruciating tenderness The correct diagnosis of amebiasis is often missed in this syndrome—in 30 cases the disease was diagnosed at autopsy and in 3 others so late that treatment could not be applied

If this type of amebiasis is the severest test of antiamebic therapy atabrine® combined with carbarsone® is the best medication available All six patients so treated recovered from the granuloma within 30 days Emetine should be abandoned and antibiotics are useful only as adjuncts to other antiamebic therapy

Amebic Hepatitis Absence of Diffuse Lesions at Autopsy and in Biopsies B H Kean[1] (Cornell Univ) found no specific diffuse hepatic lesions in (1) a large series of autopsies from an area where the incidence of intestinal amebiasis is moderately high (2) 148 persons who died of amebiasis or (3) 50 patients with the clinical pattern of diffuse amebic hepatitis who had liver biopsy The autopsy material was from 4 478 consecutive autopsies at the Board of Health Laboratory Gorgas Hospital Canal Zone The average incidence of intestinal amebiasis in this area is 10 20%

In each of the 50 patients there was substantial evidence of intestinal amebiasis current or past the clinician suspected the liver to be involved by a diffuse amebic process but not by a localized abscess Five patients had an elevated diaphragm 22 hepatomegaly and 17 hepatic tenderness 13 were jaundiced Liver biopsy in the 50 patients revealed an abscess wall in five cases three of these contained amebae and two were of pyogenic origin In 41 patients the tissue was normal Diffuse hepatitis was found in none

Of the 4 478 autopsies 13 deaths were due to amebiasis usually with amebic abscesses of the liver The histologic

(1) A M A A I I t Med 96 667 673 Nov mbe 1955

sections of the liver in all these cases were carefully reviewed No incidence of diffuse hepatitis due to E histolytica was found

Patients with intestinal amebiasis who do not have large localized abscesses may have clinical evidence of hepatic disease that often responds to antiamebic therapy *Pathologic findings do not explain this clinical syndrome of diffuse amebic hepatitis* Other investigators also have failed to demonstrate specific hepatic lesions in such patients

Failure to find a specific lesion in the liver suggests that the clinical picture of amebic hepatitis may be due to other processes The clinical symptoms the variable signs and the indefinite laboratory findings may well be the result of intestinal ulceration rather than of specific involvement of the liver

Nutrition and Intestinal Parasitism are discussed by William W Frye[2] (Louisiana State Univ) Bacteria and protozoa multiply in the body but helminths increase in number within the host only by repeated reinfection Since the number of parasites in the body is one determinant of potential damage the effect of bacterial or protozoan infection depends on host resistance to progressive increase in the number of parasites In helminthic infections however susceptibility to infection depends on resistance to reinfection from outside

Intestinal tract parasitism in most animals is restrained by a local immunity or resistance a function of the intestinal tract mucosa Interference with the nutritional status of the host may affect natural and acquired resistance to parasitic infection Resistance to helminthic infections both the somatic and intestinal phases is lowered when omnivorous hosts are maintained on diets deficient in vitamin A B complex or D or if protein is highly restricted The natural and acquired resistance of a host to its helminth parasites depends largely on the diet genetic constitution and age of the host being greatest when the diet includes adequate specific vitamins minerals and other substances

When the diet is adequate acute infection with Endamoeba histolytica is rare In a community where 40% of the population harbored E histolytica acute infections were found to be infrequent Calories and vitamins were adequate com

(2) A n New York Acad. Sc 63(rt) 175 185 195

pared to the poor diet in a similar community where acute amebic dysentery was common Although protein fat and carbohydrate intakes were about the same milk green vegetables and fruit were consumed to a greater degree in the community with little serious amebiasis Diet probably explains the different frequency of amebiasis in Bantus Indians and Europeans living side by side in Durban South Africa In maize eating Bantus fulminating dysentery is common but Africans taking a diet including fish rice and vegetables had a lower incidence of amebic dysentery In an epidemic of amebiasis traced to a water supply over 50% of individuals harbored E histolytica but none had clinical evidence of disease and only a few had amebic abscess of the liver These persons had a well balanced diet good housing and other good living conditions

Endameba histolytica produces gross changes in the intestine only if host resistance is minimal accessory intestinal bacteria are present and the diet is deficient However altering one or all of these factors in man has not controlled tissue invasion which is influenced by local conditions as well as dietary deficiency

In helminth infections specific vitamin deficiencies favor the parasite whereas a good diet potentiates host resistance

• [Somewhat divergent points of view are expressed in the preceding three articles One views amebiasis with alarm as lurking behind diagnostic corners and rarely attacked with sufficient vigor The second is iconoclastic it views with suspicion—apparently well founded—a traditionally accepted complication of amebiasis The third recognizing that amebic infestation and clinical symptoms caused by amebiasis are not identical attempts to explain the discrepancy on the basis of a nutritionally conditioned resistance of the host

Each of these concepts seems to originate from the fact that large segments of a given population may carry E histolytica but only a variable fraction have pathologic changes that can be ascribed to the parasites We thus have two camps the amebaphobes (Gastroenterology 30 322 375 1956) who ascribe every last symptom of the ameba carrier to his infestation and the anti amebaphobes who believe that the ameba carrier suffers functional symptoms as does the rest of the population and that the explanation of these symptoms on the basis of amebiasis harms the patient and imperils his successful therapy (see 1954-55 YEAR BOOK p 539 and 1955 56 p 538)

Dr Frye offers one explanation why amebiasis may be a more serious clinical problem in one population than in another but a missionary physician practicing for over 20 years in Angola roughly half way on a straight line drawn between Durban and Nigeria, finds the situation reversed. The native population poorly provided with calories and protein, carries E histolytica with little difficulty the well nourished white resident seems to fall ready prey to the disease —Ed]

Observations on Temperature of Human Liver Parenchyma were made by W Graf I G Porje and A M Allgoth[3] (Stockholm) After an ordinary liver biopsy the outer needle was left inserted in the parenchyma and an insulated wire

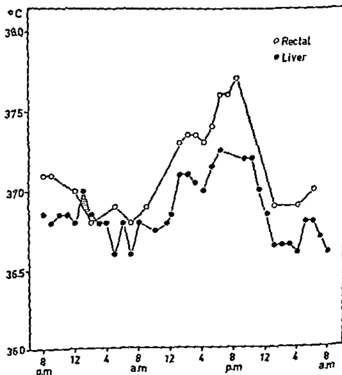


Fig 9 —D l rhythm of rect l t l t mpe t re n o e pat t (Co r t sy of Graf W t al G troe t rolog a 83 33 243 1955)

ending in a thermosensitive junction pushed forward to the end of the biopsy needle which was then withdrawn The temperature indicator remained in the liver and was fixed to the skin with adhesive plaster Recordings were made at intervals of 5 60 minutes for 1 3 days

(3) Gastroe t rol g 83 33 243 1955

The diurnal rhythm of rectal and liver temperatures was studied in six patients The liver temperature was parallel to but 0 2-0 6 degrees C lower than the rectal temperature (F g 92) However in one patient it was higher for a brief period and in another the two temperatures were temporarily the same in two separate periods

In four patients artificial fever was induced by intravenous injection of 0 7 ml of a preparation containing killed bacteria All had a temperature reaction In two rectal temperatures remained higher than liver temperatures during the whole period of measurement in one the organ temperatures crossed for a short time and in one the liver temperature remained higher for about three hours The rectum liver temperature difference was approximately the same irrespective of the general body temperature level

Contrary to general belief rectal temperature may not be representative of body temperature level

Note on Pathogenesis of Jaundice is presented by Torben K With[4] (Svendborg Denmark) The poison icterogenin a triterpenoid acid obtained from the South African plant lippia rehmanni Pears is icterogenic and when given to sheep produces jaundice colorless bile and some suppression of bile secretion This icterogenin poisoning is completely reversible accompanied by neither macroscopic nor microscopic biliary occlusion histologic lesions in the liver parenchyma nor hemolysis

Jaundice following icterogenin poisoning seems to be a pure form of retention jaundice However contrary to current views about retention jaundice it becomes intense within 24 hours and the direct diazo reaction is frankly positive Until the present the only pure retention jaundice experimentally producible was that following partial or complete hepatectomy This type is not an ideal object of study since most of the bilirubin production is located in the part of the reticuloendothelial system involved in removal of the liver

Before it can be assumed that the jaundice after lippia poisoning is a pure retention jaundice the possibility must be considered that icterogenin does not paralyze the secretory power of the liver but changes the normal secretory pathway from blood to bile to an abnormal pathway from blood to lymph Studies with icterogenin may throw light on the

(4) Acta med sc d 15 239 24 1955

forms of jaundice in which neither biliary occlusion parenchymal liver damage nor increased bile pigment production can be demonstrated

Radioactive (I^{131} Tagged) Rose Bengal Uptake Excretion Test for Liver Function Using External Gamma Ray Scintillation Counting Technics is described by George V Taplin Orvell M Meredith Jr and Harold Kade[5] (Univ of California Los Angeles) After the dye is given intravenously a suitable gamma ray counting device placed over the liver area registers a curve composed of a relatively steep upward slope expressing the rate of hepatic uptake of dye and a slower downward component expressing gradual removal of the dye via the bile The plateau at the peak of the curve represents the balance of uptake and excretory mechanisms *the height of the peak thus indicates hepatic efficiency in taking up the radioactive test substance rapidly*

In normal rabbits the liver uptake curve reaches a maximum in 10 25 minutes and is reciprocally related to the rate of blood clearance Rose bengal both in aqueous solution and mixed with bile after passage through the liver of one rabbit is not absorbed from the gastrointestinal tract of normal rabbits Liver uptake excretion abnormalities for tagged rose bengal can be detected as soon as one hour after a dose of 840 mg /kg carbon tetrachloride Histologically the degree of fatty degeneration of the polygonal cells parallels the decrease in maximum amplitude of the dye uptake curve

The phagocytic action of the reticuloendothelial system in several groups of rabbits was blocked by intravenously administered colloidal thorium dioxide India ink hemolyzed erythrocytes and gelatin and by whole body irradiation None of these animals had abnormal radioactive rose bengal liver uptake excretion patterns The uptake and excretion of rose bengal seem to be exclusive functions of the polygonal cells of the liver with little participation by the reticuloendothelial system

Reliable and reproducible results were obtained in human beings by positioning the lead collimated counter (sodium iodide crystal) on the right anterolateral aspect of the chest wall over the upper margin of the liver as determined by percussion and directed away from the gallbladder area Be

(5) J Lab & Clin Med. 45 665 678 May 1955

tween 0 5 and 5 0 mg dye was given intravenously the total radioactive dose being held constant at 5 µc

Tracings from patients with both acute and chronic hepatitis deviated from normal The uptake slopes were depressed and the amplitude of the peaks was generally lower than in normal individuals In some the excretion rates were impaired

The te t measures polygonal cell function directly rather than by changes in the blood and eliminates repeated venipunctures The rate of uptake and time required for excretion from the liver is graphically registered The dye is safe because of the minute quantities required and its low toxicity even in biliary tract obstruction The test gives information concerning liver circulation as well as biliary tract patency and appears many times more sensitive than nonradioactive dye te t

• [This ingenious technic may be useful under various conditions especially in the field of clinical investigation It has its difficulties however For one the lightest shift in the patient s pos t on with respect to the counting device may distort the uptake excretion curve by exposing the counter to radiations emanating from dye collecting in the gallbladder and it i not ea y for a patient to remain immobile for a period of one to t o h r —Ed]

Evaluation of Factors Influencing Discriminative Effectivene s of a Group of Liver Function Tests —II *Normal limits of 11 representative hepatic tests* were determined by Leslie Zieve and Earl Hill[6] (Univ of Minnesota) in a study on 720 healthy gainfully employed males The frequency distributions were plotted for each test and the limits of normal determined (see table) The 10 5 and 1% points of each distribution were also listed Values falling below the 1% point were considered definitely abnormal A zone of doubtful abnormality was established between the 1% point and a point which fell at or between the 5 and 10% points the exact position of the point varying somewhat from test to test and depending on the test s reliability and the shape of its distribution

In general the limits of normal were higher than those previously accepted The sample was relatively large and unselected in contrast with the small selected groups of normal individuals typically utilized It seems likely that the results

(6) G t oe t rol gy 28 766-784 M y 1955

LIMITS OF NORMAL OF VARIOUS QUANTITATIVE LIVER FUNCTION TESTS*

Test	Zone of Doubtful Abnormality	Zone of Definite Abnormality
1B mg %	0 20-0 25	>0 25
TB mg %	1 0-1 5	>1 5
TT units	5 0-8 0	>8 0
ZT units	12 0-15 0	>15 0
% CE		
Lower limits	72 70	<70
Upper limits	8-80	>80
BSP %		
No weight adj	8 14	>14
After weight adj	7 13	>13
HA gm		
Lower limit	0 90-0 60	<0 60
Upper limits	1 40-1 60	>1 60
GT mg %	30-42	>42
UU mg /day	3 0-5 5	>5 5
LCP μg /day		
Lower limits	110-80	<80
Upper limit	275-360	>360

1B e um 1 ubin on m ute TB t t l b l ubin TT thymol t b d ty ZT n s lfat t b d ty (F h l t l st BSP b m ulfale n t t on HA nt a enou h ppt c a d GT nt n u g l cros t l an e UU urin u b l og n ULP u e c p po phy n

of the present study approximate true normal limits of these tests more closely than any heretofore reported but they must be looked on as of temporary and limited value because technics change rapidly and vary widely Full value of such a study will not be realized until standardization of liver function tests is achieved

III Relative effectiveness of hepatic tests in cirrhosis was studied by Zieve and Hill[7] using 100 normal healthy men and 41 patients with cirrhosis The widespread use and multiplication of available liver function tests made their objective evaluation mandatory Many analyses of test results in cirrhosis have been reported but a sufficiently large number of tests were not performed at the same time on the same patients and quantitative interrelationships among the tests were not taken into account

Cephalin cholesterol flocculation and colloidal red flocculation could not be tested

All the tests effectively differentiated normal subjects from patients with cirrhosis but the extent to which they separated

(7) Ga t oent l gy 8 785 80 May 1955

the two groups varied greatly Nine tests in the order of decreasing indexes could be grouped roughly into four levels of discriminative effectiveness Intravenous galactose tolerance and hippuric acid were approximately three fourths as effective as the bromsulfalein retention (BSP) zinc sulfate turbidity urine coproporphyrin and per cent cholesterol esters approximately three fifths and urine urobilinogen thymol turbidity and total bilirubin approximately two fifths as effective The best single test for detecting abnormal or specifying normal individuals is the BSP test it is also the best single test for group comparisons

Only four of the nine tests—BSP zinc sulfate turbidity intravenous hippuric acid and urine coproporphyrin—were significantly discriminatory The other five—total bilirubin thymol turbidity per cent cholesterol esters intravenous galactose tolerance and urine urobilinogen—could differentiate between the abnormal and normal groups but contributed little beyond that of the significant four tests Only two tests BSP and urine coproporphyrin were unequivocally significant independently Tests which on the surface appear to represent different functional changes actually are consequences of a common set of factors The large battery of tests is superfluous since beyond the significant few additional tests contribute no new information

The combination of tests BSP zinc sulfate turbidity intravenous hippuric acid and urine coproporphyrin or the combination LSP zinc sulfate turbidity and urine coproporphyrin is somewhat more specific and more sensitive than the BSP test alone and will probably be useful if the suspicion of liver disease remains in patients with normal BSP

• [The orientation of this study must be kept in mind If a patient with cirrhosis happens to be quite jaundiced the BSP test will of course serve to discriminate between him and a normal subject but from a clinical point of view it will provide little information either for diagnosis or for evaluation of the degree of liver damage —Ed]

Practical Considerations of Diseases of Porphyrin Metabolism Porphyria and Porphyrinuria are reviewed by F William Sunderman Jr and F William Sunderman[8] (Jefferson Med College) The term porphyria denotes disease states with relatively large amounts of urinary uroporphyrins preformed or as their precursor porphobilinogen Urinary and fecal coproporphyrins also are usually increased

(8) Am J Cl P th 25 1 31 1 5 November 1955

Porphyrinuria denotes conditions with abnormally large amounts of urinary porphyrins other than uroporphyrin The coproporphyrins predominate In man porphyrinuria is secondary to various pathologic conditions

The study of tissue porphyrins has divided the porphyrias into two major clinically useful groups erythropoietic and hepatic An abnormal production of uroporphyrins is believed to occur in the bone marrow in the erythropoietic form and in the liver in the hepatic form The hepatic form may be subdivided into the paroxysmal photosensitive and combined paroxysmal and photosensitive forms Some persons apparently in good health excrete abnormally large amounts of uroporphyrin They are often related to patients with porphyria and are considered as having latent porphyria

The salient features of erythropoietic porphyria are an onset in infancy or childhood occurrence more commonly in males symptoms of photosensitivity skin susceptible to trauma hypertrichosis red teeth melanosis and red urine with findings of bullous vesicular lesions hemolytic anemia and splenomegaly The cause is a genetic enzymatic defect in the synthesis of hemoglobin The diagnostic findings are uroporphyrin I and coproporphyrin I in urine no porphobilinogen and fluorescence of normoblasts in the marrow *Splenectomy has benefited a few patients*

The hepatic porphyrins probably originate from genetically or chemically induced disturbances of porphyrin metabolism in the liver Liver catalase may be involved since this enzyme is decreased in rabbits with experimental porphyria A syndrome *resembling paroxysmal porphyria has been produced* by administering sedormid® (allyl isopropyl acetyl carbamide) in rabbits rats and chick embryos

Paroxysmal hepatic porphyria has its onset during the ages 20-40 occurs predominantly in females (61%) presents with gastrointestinal symptoms in 95% *including pain vomiting* constipation diarrhea neurologic symptoms peripherally in 72% and cranially in 51% with motor weakness hyporeflexia muscle pain and sensory loss predominating and mental symptoms of psychoses delirium and irritability in 80% Miscellaneous symptoms include hypertension *in 49% tachy*cardia in 51% red urine in 69% fever in 36% pigmentation in 13% and hepatic dysfunction There is no photosensitivity

The diagnostic findings are porphobilinogen in urine uro and coproporphyrins III and I (Zn complex) in urine and feces porphobilinogen and uroporphyrin in liver biopsy Therapy includes tetraethyl NH_4Cl splanchnicectomy procaine intravenously ACTH and cortisone

Photosensitive hepatic porphyria usually occurs after age 20 usually in men The symptoms include photosensitive skin susceptible to trauma abdominal colic melanosis pigmentation hypertension psychosis neuritis and red urine The cause is a genetic or chemically induced disturbance of hepatic porphyrin metabolism associated with hepatic insufficiency alcoholism diabetes or syphilis The diagnostic findings are uro and coproporphyrins III and I (Zn complex) in urine and feces porphobilinogen occasionally present and uroporphyrin in liver biopsy Therapy includes a high protein diet vitamin B_1 and abstinence from alcohol and barbiturates

In the combined paroxysmal and photosensitive hepatic form of porphyria which is relatively uncommon the photosensitive symptoms often predominate at one period in the patient s life and the paroxysmal features at another

Coproporphyrin I and III are found in small amounts in the urine of normal persons Abnormal amounts of ether soluble porphyrins (chiefly coproporphyrin) are commonly present in the urine in a wide variety of pathologic and physiologic conditions

Increased urinary coproporphyrins is associated with chemical toxicity from metals (Pb As Hg Bi Cu Fe Au Ag Zn P) sedatives (veronal® sulfonal®) sulfonamides alcohol and organic compounds (TNT CH_3Cl CCl_4) with hypermetabolism of fevers thyrotoxicosis and exercise with hepatic diseases of cirrhosis infectious hepatitis and carcinomatosis with hematologic conditions such as pernicious anemia the hemolytic anemias hemochromatosis leukemia and Hodgkin s disease with hypovitaminoses of pellagra and ariboflavinosis and may appear as asymptomatic idiopathic coproporphyrinuria

* [This is a handy list for those not dealing routinely with the abnormalities of porphyrin metabolism It may be particularly useful to the gastroenterologist confronted by one of Robert Kark s termagants—the resentful irascible unpredictable vituperative woman with porphyria and multiple abdominal scars testifying to her stubbornness in seeking relief from pain (M Clin North America 39 11 January 1955) —Ed]

Posthepatitic Hyperbilirubinemia was observed by H Kalk[9] (Kassel Germany) during the last 5½ years in 161 patients It affects principally young men under 40 who appear to be neurasthenic or hypochondriac Only a fifth of the patients were women Most patients had had epidemic hepatitis 6 months to 15 years earlier but in a few history of hepatitis was lacking Intermittency of symptoms was an outstanding feature Nausea loss of appetite fatigue depression irritability pressure under the right costal margin a feeling of fulness and gastrointestinal disturbances with diarrhea and constipation were noted Yellow tinged ocular conjunctivas were usually present with the symptoms Exacerbations were related to alcoholic intake dietary indiscretions and overwork

Increase in indirect serum bilirubin levels to 1 5-4 mg/100 ml is the significant finding Direct bilirubin reaction is rare and then only slight Bilirubin content of serum may change within days or even hours Blood sedimentation rate is conspicuously slow Bromsulfalein excretion was accelerated in a fourth of the patients in others it was normal or slightly delayed In about a third there were signs of increased hemolysis with decreased resistance of red cells (below 0 5 0 3% NaCl) increased reticulocytes (over 10%) and decreased erythrocyte diameters In some instances sternal puncture showed increased erythropoiesis Serologic changes (Coombs test cold agglutinins) were absent Serum protein level was within normal range Urine contained no bilirubin

Liver biopsy in 82 revealed absence of inflammatory changes typical of hepatitis but definitely increased activity of Kupffer cells Fat in liver cells was slightly increased in about a fourth Most impressive histologic finding was increased deposition of brown pigment with predilection for the central lobe (in some severe cases involving the entire lobe) This pigment which stained brown with hematoxylin eosin blue green with Pappenheim stain and reddish brown with iron stain is also increased in Meulengracht s disease congenital hemolytic icterus and siderophilia (hemochromatosis) It is doubtless identical with that described by others as iron free pigment in siderophilia or as unknown pigment of a new liver disease The authors believe that this is a par

(9) Ga t oent r f z 84 07 225 1955

ticular form of masked iron bound to protein or lipoid bodies in such a way that it does not give a typical iron reaction

Prognosis is good Progression to severe hemolysis cirrhosis or chronic hepatitis has not been observed Therapy consists of (1) reassuring the patient that he does not have severe liver disease (2) milk and vegetable diet with decreased intake or in severe cases complete avoidance of meat protein being supplied by cheese cottage cheese and yogurt (3) a gastric mucosa preparation or one containing vitamin B_1 intrinsic factor and yeast autolysate (4) avoidance of alcohol of undue bodily exertion of self pampering and of invalidism

Symptoms are similar to those of disorders of porphyrin metabolism Clinical symptoms are most likely produced by temporary accumulation of porphyrins subsequent to disturbed hemosynthesis Disturbance of hemosynthesis by liver injury may result in surplus of protoporphyrin which is removed either by transformation into uroporphyrin and excretion in urine or by transformation into bilirubin If such is the case hyperbilirubinemia may result from combined effect of destruction of hemoglobin and increased formation of bilirubin from protoporphyrin

• [This article attempts to draw together the various syndromes associated with hyperbilirubinemia of the indirect reacting type (known in the United States chiefly as Gilbert s disease familial nonhemolytic jaundice and constitutional hepatic dysfunction) into one syndrome differing quantitatively but not qualitatively and representing on the whole a residual of an attack of hepatitis On pathologic grounds Kalk includes the syndrome described by Dubin and Johnson (1955 56 YEAR BOOK, p 549) but the severity of hepatobiliary abnormalities in Kalk s cases does not seem as str king as in those descr bed by Dub n and Johnson —Ed.]

Posthepatitic Syndrome Laslo Kallai[1] (Univ Hosp Zagreb) studied 32 men and 10 women with chronic mild hyperbilirubinemia confirming the sex ratio found by other authors In 31 of the patients indications of previous manifest hepatitis were present 1 10 years before hospitalization

Characteristic symptoms were lassitude and fatigue even in patients averaging 12 14 hours in bed The slightest exertion markedly increased the fatigue Pain occurred most frequently in the right upper quadrant of the abdomen or the right lower chest and occasionally in the right lumbar region The most frequent complaint was a sensation of heaviness tenseness and stitch The pain at times was intense but

(1) G t oe ter l g 83 7799 19 5

rarely colicky and was *unrelated to respiration* It could occasionally be brought on by breathing deeply or lying on the right side it often increased with exertion and after food intake Greasy food was not tolerated and anorexia nausea vomiting and dyspepsia were common Many patients had insomnia nervousness and excitability Tremor of the hands was observed and vasomotor changes induced profuse perspiration with cold clammy hands Mental depression and fear of deterioration often were present Headache and a sensation of pressure in the occipital region were noted and a few patients had sexual neuroses

Physical examination revealed palpable painful liver edges in all the patients and enlargement by one fingerbreadth in one In 6 patients who had hepatitis splenomegaly was also present but was found in only 2 of the 11 without hepatitis

Sedimentation rate red blood cell count leukocytes and sternal marrow findings were normal The Coombs test for acquired hemolytic jaundice gave negative results Serum iron ranged from slightly diminished to increased values Urinary urobilinogen was normal Serum bilirubin ranged from 1 to 5 mg /100 ml and varied from day to day The severity of jaundice could be increased by excitement infection insomnia alcohol greasy food or mental or physical exertion Patients with and those without previous manifest hepatitis had similar proportions of direct and indirect bilirubin

Flocculation tests thymol turbidity and gold sol flocculation were normal Total proteins and albumin were normal but globulin was elevated in half the patients Liver biopsy in 28 patients revealed well preserved trabecular structure cells of equal size normal protoplasm and uniform color Steatosis of the liver was noted in 15 patients discrete in 9 and slightly more marked in the others It was present in 11 of the 22 patients with hyperbilirubinemia who had had manifest hepatitis in the past Bilirubinemia was not correlated with the presence or intensity of steatosis

The posthepatitic syndrome develops after acute hepatitis for unknown reasons Insufficient rest and unsatisfactory food during the acute stage of hepatitis may contribute So called constitutional dysfunction of the liver and familial cholemia probably are complications and sequelae of an anicteric form of infectious hepatitis and not diseases *sui generis*

Although the prognosis of posthepatitic sy[illegible] is favor

able and the complications benign it is associated with variable degrees of invalidism

• [To prevent the posthepatic syndrome this author calls for bed rest in the treatment of acute hepatitis Bed rest is the most important part of the treatment its duration should be at least two months If bilirubin values do not return to normal levels if flocculation tests remain positive *or if signs of active inflammation are revealed by biopsy bed rest must* be continued until all the aforementioned clinical and laboratory symptoms have disappeared. Is he right? Not according to what follows —Ed.]

Treatment of Acute Infectious Hepatitis Controlled Studies of Effects of Diet Rest and Physical Reconditioning on Acute Course of the Disea e and on Incidence of Relapses and Residual Abnormalities are reported by Thomas C Chalmers Richard D Eckhardt William E Reynolds Joaquin G Cigarroa Jr Norman Deane Robert W Reifenstein Clifford W Smith and Charles S Davidson The opportunity for a statistical re evaluation of the relative effect of bed rest and diet in the treatment of infectious hepatitis was afforded by the establishment of a center in Kyoto Japan for the treatment of American soldiers contracting the disease in Korea Patients were admitted to the various treatment groups at random and were followed by carefully standardized clinical and laboratory observations Criteria for treatment effect were (1) time between admission and a normal total serum bilirubin and bromsulfalein test (2) incidence of relapses during convalescence and (3) occurrence of disability and hepatic functional abnormalities on follow up examination

In the first of three studies 65 patients were assigned to each of four treatment groups (1) strict bed rest and a forced high protein high calorie diet with choline and vitamin supplements (2) strict rest and regular hospital diet eaten ad lib (3) ad lib bed rest and forced diet and (4) ad lib rest and ad lib diet Patients on the strict bed rest regimen were allowed one trip to the bathroom per day Those on ad lib rest were allowed to be up and around their ward at will but were required to rest in bed for an hour after each meal Carefully conducted bed checks revealed marked differences in physical activity between the two groups The mean durations of illness however were the same Patients on the forced diet had a duration of illness 7 days (standard error 1 6 days) less than that of the patients fed the regular diet ad lib Asymptomatic relapses characterized by return of an abnormal bromsulfalein test occurred in 5% of each group

J Clin I t. 34 (pt 2) 1163 1235 J ly 1955

In the second study, designed to detect whether the previously observed dietary effect was related to the protein calorie or supplement contents of the diet, 48 patients were assigned to each of the following strictly enforced dietary regimens (1) 4 000 calories 19% protein calories, (2) 4 000 calories 11% protein calories (3) 3 000 calories 19% protein calories and (4) 3 000 calories 11% protein calories Half of each group received supplements of choline and vitamins Patients on the 19% protein diets convalesced in 28 days 6

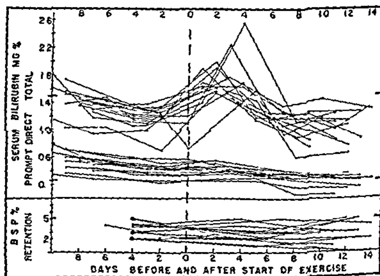


Fig 93—Ch g n rum b l rub n and bromsulfalein tests of 14 patients in ea ly e e gro p whos t t l erum b l rub os abo e rmal (C u t y of Chalmers T C s l J Clin In e t 34 (pt. 2) 1163 1235 J ly 1955)

days (S E 2.2 days) sooner than those on the 11% protein diets The durations of illness were similar for the patients eating high and low calories and for those receiving supplements and placebos The occurrence of relapses during convalescence were likewise similar

In the third study half of the second study patients were started on a program of strenuous physical rehabilitation as soon as their serum bilirubin and bromsulfalein tests were normal the other half were kept in the hospital as controls for 8 days and then exercised Minor changes in symptoms signs and liver function tests occurred amo former

group when compared with the controls but the abnormalities disappeared while the exercise program was continued and the patients were the same by all criteria at the end of the observation period

Of 188 randomly selected patients 97% were examined 6 18 months after return to duty No deleterious effects of ad lib rest were detected The high protein group in the second study had slightly more abnormalities on examination but the significance of these findings is unknown No patients had definite recurrences of their jaundice

It was concluded that patients convalescing from infectious hepatitis could safely be allowed to be up and about their hospital ward or home regardless of the degree of jaundice Elimination of the prolonged disability caused by strict bed rest may thus shorten the over all duration of the illness The forcing of a high protein diet early in the illness shortens the duration of jaundice but is difficult to accomplish and may be hazardous in the very sick patient

Effects of Dietary Protein Lipotropic Factors and Re alimentation on Total Hepatic Lipids and Their Distribution are reported by C H Best W S Hartroft C C Lucas and Jessie H Ridout[3] (Univ of Toronto) In the livers of rats maintained on a low protein diet the consequent accumulation of lipid has a different distribution than the hepatic fatty infiltration that develops during choline deficiency In rats fed basal diets low in casein most of the stainable fat in the livers was in the periportal areas and only a trace in the centrolobular These diets contained considerable methionine probably sufficient as a choline precursor to keep the centrolobular areas clear As long as the protein in the diet was low even large doses of choline were unable to prevent some deposition of abnormal fat

A prolonged low protein diet free from choline produced a very fatty liver with some of the lipid in the periportal areas but most in the centrolobular When the protein intake was made adequate the rats ate twice as much and began gaining weight Coincident with this sudden increase in food consumption there was during the first three days a dramatic increase in total liver lipids all in the periportal areas With continued intake of the same amount of food the abnormal fat soon disappeared

(3) Brit M J 1 1439 1444 J 18 1955

The deleterious effect of low protein diets may be related to some deficiency of essential amino acids Protein inadequacy in protecting the liver appears to begin at about 12% in the diet when casein is fed and below 6% for fibrin Choline inadequacy begins at about 0 12% (expressed as chloride)

The term fatty liver has different connotations Only when the analytical figure is increased appreciably above the normal range would the chemist describe the liver as fatty" The pathologist may see stainable fat sometimes in considerable amount before the extractable lipids are significantly increased The extraction procedure must be known also the base toward which the analytical data applied such as fresh dry fat free or dry and fat free tissue

In choline deficiency lipid values may reach 15-40% of fresh liver weight Figures of 25-45% have been reported in rats fed diets low in protein but these were expressed in terms of dry liver weight When referred to fresh weight the total hepatic lipids in rats on protein deficient diets are no more than 8 18% usually below 14% These are fatty livers but mild compared to those in choline deficiency If choline is made available fibrosis or cirrhosis of the liver is not produced even after a year of low protein diet

Clinically it has been difficult to show the lipotropic efficacy of choline and methionine partly because the human liver may be damaged by multiple deficiencies and partly because most hospital diets supply an abundance of lipotropic agents The transient increase in liver lipids observed when protein intake was suddenly improved may have clinical counterparts in the treatment of alcoholic subjects with certain good diets Factors other than protein and choline deficiency may determine the deposition and localization of fat in the liver

• [One objection to applying the concept of nutritional liver disease as it develops in rats to cirrhosis in man has been the fact that lipid accumulates near the central vein in choline deficient rats but preponderantly at the periphery of the liver lobule in alcoholics Perhaps the experiments here reported will help bridge the considerable gap between human liver disease and that induced in rats by grossly abnormal diets —Ed]

Acute Fatty Liver of Pregnancy obstetric acute yellow atrophy was first described in an article concerned with the lesions and clinical syndrome of delayed chloroform poisoning According to H C Moore[4] (The Rotunda Dublin)

(4) Ir b J M Sc pp 451 458 Oct ber 1955

obstetric acute yellow atrophy differs morphologically from chloroform poisoning and other hepatic necroses in that the lesion is one of fatty change and the liver is not necrotic Nevertheless there is severe liver failure which often terminates fatally

At 36-40 weeks gestation severe vomiting and epigastric pain occur followed in a few days by jaundice The symptoms progress rapidly jaundice becomes intense vomitus is coffee ground material and headache is sometimes present After 7 10 days the patient is delivered of a stillborn fetus becomes comatose and dies within 3 days In a distinctive clinical sub group the illness is heralded by jaundice in the early puerperium within 24 hours Toxemia of pregnancy is not a frequent complication occurring in only 3 of 18 patients Liver failure is severe 15 of 18 cases ended in coma and death Neurologic changes such as confusion delirium mania and convulsions have been noted in fatal cases and in patients who have recovered

At autopsy lesions are found only in the liver except for hemorrhages in various sites The pancreas extrahepatic biliary system and kidneys are normal and the lesions of Wernicke s encephalopathy are not found The liver is usually golden yellow and slightly small and weighs less than normally Cells around the central vein are bloated and foamy The cytoplasm is stretched in thin strands between innumerable fine vacuoles of neutral fat A rim of periportal liver cells almost always remains normal Both normal and affected cells contain bile pigment Bile thrombi are present between liver cells of the affected centrolobular zone to a less extent between normal cells of the periportal area but not in bile channels of the portal tracts Liver tissue is not necrotic This type of fatty liver with clinical liver failure occurs only in pregnant women

None of the patients had chemical poisoning leptospirosis or infective hepatitis The pancreas and the extrahepatic biliary tract were normal In three patients thymol turbidity was normal and serum alkaline phosphata e elevated The obstructive picture in acute fatty liver of pregnancy has been considered due to obstruction at the cell level a hepatocellular obstruction but no evidence of such has ever been found

The cause of uremia in acute fatty liver is unknown but

it may be related to the vomiting Clinically urine output is well maintained and histologically there is no renal damage The three main complications of this type of hepatic failure are hypoglycemia hypopotassemia and a hemorrhagic tendency due to either a prothrombin or a fibrinogen deficiency Presumably any one of these disturbances may kill the patient

The liver lesion might be due to some unknown agent e g an infection capable of preventing the function of the liver cell but not of killing the cell Whatever the cause possibly an exogenous or endogenous lipotrope deficiency it manifests itself as fatty accumulation

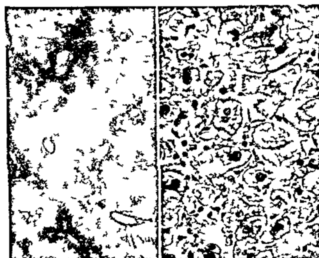
Acute Fatty Metamorphosis of Liver Associated with Pregnancy Distinctive Lesion observed in 3 cases is reported by William B Ober and Philip M LeCompte[5] (Boston) with a review of 11 previously reported cases Jaundice clearly of parenchymatous (hepatocellular) type appears late during the last trimester and is accompanied by signs symptoms and laboratory indications of acute liver failure Patients become progressively worse even after delivery and die in hepatic failure Of 14 patients 13 died (92 9%) Though clinically the disease is not distinguishable from fulminant epidemic hepatitis pathologic findings are different *There is diffuse* fatty metamorphosis of the liver with preservation of lobular structure and sparing of the peripheral portion of the lobule (Fig 94) Necrosis is absent or minimal in the paracentral zone Infiltration may be absent or a sparse randomly distributed infiltration of a few lymphocytes an occasional polymorphonuclear leukocyte and a rare eosinophil may be noted

With use of 5 49 Gm Formalin fixed liver (Case 2) values of total lipids were 13 04% of total fatty acids 10 8% of phospholipids 0 23% of total cholesterol 0 19% of free cholesterol 0 14% and of cholesterol esters 0 05% which correspond closely with values for hepatic lipids in ethionine treated fasted female rats In both instances liver fat is increased due to increase in *fatty acids In these cases intracellular lipid appears quite regularly as fine droplets* giving a honeycombed appearance to the cytoplasm (Fig 95) The more usual large single intracytoplasmic vacuole which pushes the nucleus *off to one* side is conspicuously absent Whether this is an

(5) Am J Med 19 743 759 N mbe 1955

artefact of rate of intracellular lipid accumulation or a specific property of fatty acids in contrast to neutral fats is speculative

There may or may not be fatty metamorphosis of the renal tubular epithelium In one patient degenerative changes were sharply limited to the columns of Ferrein involving only the terminal portion of the proximal convoluted segment In an



F 4 (l ft) —P l f f ty m tam rph n tral tw th d f l bul d d by da k m f p d l ll H m yl eo
F g 95 (ght) —L ll w th f tty m t m ph h w g m lt pl fi l d t d g yt pla f th cell te b l t ll H m t l eo n. (Co rt y f Obe W B d LeC mpt P M Am J Med 19 743 758 N mbe 1955)

other the lesion in the tubular epithelium was less sharply localized fine fatty vacuolation of many parts of the proximal convoluted segment but no necrosis was noted

None of the three patients showed evidence or history of dietary deficiency or of exposure to or ingestion of an exotoxin It is inferred that the pathogenesis of this obscure and uncommon lesion lies in some humoral agent which is present because the patient is pregnant or exerts an abnormally destructive effect during pregnancy The endogenous metabolic aberration produced by this hypothetical agent possibly produces fatty changes in the liver by interference with en

it may be related to the vomiting Clinically urine output is well maintained and histologically there is no renal damage The three main complications of this type of hepatic failure are hypoglycemia hypopotassemia and a hemorrhagic tendency due to either a prothrombin or a fibrinogen deficiency Presumably any one of these disturbances may kill the patient

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(5) Am J Med. 19 743 758 N mbe 1955



F g 96 (top) —P dod t l b dd g oc t d w th p kl d filt t f po t l ea by lymph yt l t t terl b l d t l m y b d tly b po t l d l (l w t) R mbl t p ph l f g f ll rd pp ent R l d f m 3 5
F g 97 (b ttom) —Ob t t b l t s I t l b l d t d t d d by m f t b l d th t f t h l g t I fl mm t y d t th ghout p rt l mp d m ly f t ph l Th mp ying p eudod t la b dd g R d ed f om x 3 5
(C rt y f G ll E A d B t H A J Cl P th 25 1113 1127 O t b 1955)

zyme systems speculatively those concerned with transmethylation

* [Here appears to be a clearcut syndrome clinically and pathologically not generally recognized Two out of three recent textbooks on diseases of the liver fail to mention it Except for the question of associated renal lesions the two previous articles seem to agree remarkably particularly with respect to the foamy fatty infiltration of the liver cells near the central vein —Ed]

Hepatitis with Manifestations Simulating Bile Duct Obstruction So called Cholangiolitic Hepatitis Edward A Gall and Herbert Braunstein[6] (Univ of Cincinnati) describe the morphologic features of this clinical syndrome as it occurred in 14 patients with jaundice whose clinical course excluded extrahepatic biliary tract obstruction Surgical exploration was fruitless in seven and seven recovered after expectant care only The pathologic features of acute viral hepatitis in 30 patients and of biliary obstruction in an additional 20 patients were compared

In viral hepatitis the portal area invariably contained exudate usually composed of lymphoid elements In patients who recovered promptly parenchymal damage was manifested by minute foci of necrosis often limited to single cells with no predilection for specific portions of the lobule Parenchymal injury was sometimes inconspicuous but careful examination revealed necrosis of individual cells with satellite clusters of lymphocytes ignored in casual survey The intact interlobular ductule appeared to serve as a nidus about which the exudate was more heavily concentrated Almost all the cases had intralobular bile stasis (usually considered an insignificant feature of viral hepatitis) more apparent when parenchymal alterations were less prominent The main interlobular ductule was readily identified and had no dilatation stasis intraluminal exudate or evidence of reduplication

In hepatitis simulating biliary obstruction the pattern of inflammation in portal areas was the same Periductal concentration of the exudate (pericholangitis) altered the frame of reference but focal necrosis eosinophilic hyaline bodies intralobular clusters of lymphocytes and balloon cells devoid of fat could be detected invariably Centrolobular bile stasis and perilobular pseudoductular budding were usually more prominent (Fig 96)

In patients with extrahepatic obstructive icterus cytologic

(6) Am J Cl P th 25 1113 1127 O t be 1955



F g 96 (top) —P d×d t l b dd g oc t d w th p kl d filt t f portal by l mphocyt I t t t l b l d t l m y b ee d tly bo port l d l (l w ent) R mbl t p ph l f g f ll d pp t R d d f m ×3 5

F g 97 (bot om) —Ob tr t b l t I t l b l d ct d t d d by f tat b l d th at f t h l g I fl mm t ry d t th ghout po t l or p d m ly f n t ph l Th mp y g p eudod t l b dd g R d d f m ×3 5

(Courtes f G ll E A d B u t H Am J Cl P th 2 1113 1127 O t b 1955)

alterations of hepatitis were not present and portal area exudate was spotty and often neutrophilic. The exudate was intimately related to the interlobular duct and leukocytes were observed migrating through its wall. True ductal proliferation was distinguishable by distortion, dilatation and branching of the small interlobular duct and by intraluminal accumulation of purulent exudate, bile or both (Fig 97). This was never noted in any form of primary hepatitis. The "bile lake," probably a coalescence of static bile released by disruption of distended canaliculi, and its accompanying feathery degeneration (sometimes designated a "bile infarct") were pathognomonic of extrahepatic biliary obstruction.

Clinical manifestations of biliary obstruction in hepatitis have been attributed to specific impairment of cholangioles. Not clearly demonstrable in sections of normal human tissue, the cholangiole has been presumed to exist as a connecting piece between the unlined intralobular bile capillary and the definitive interlobular duct coursing through the portal tract. The present investigation, however, indicates that hepatitis simulating biliary obstruction in conjunction with pathognomonic histologic changes (cholangiolitic hepatitis) is not an entity. Pericholangitis, bile stasis and pseudoductular budding, though common with this syndrome, are by no means invariable and are encountered in patients with classic viral hepatitis but without suspicion of obstruction. This puzzling clinical syndrome cannot be explained morphologically.

• [The authors thus hold that the clinical, biochemical and histologic features of classic viral hepatitis, on one hand, and of cholangiolitic hepatitis, on the other, are merely variants of the same process. If this is the case, the pathologist, on the basis of a hepatic punch biopsy, should be able to distinguish cholangiolitic hepatitis from the lesions occurring in surgically correctible obstructive jaundice—and this, the authors imply, they can do. Yet they mention only one finding as pathognomonic of extrahepatic biliary obstruction, namely, the "bile lake and its accompanying feathery degeneration," certainly not an invariable finding in those jaundiced because of choledochal obstruction. The clinician is hard to convince; he still suspects that in certain cases the differential diagnosis of "medical" versus "surgical" jaundice will continue to stump the pathologist as well as himself.—Ed.]

Liver Decompression by Common Bile Duct Drainage in Subacute and Chronic Jaundice: Report of 60 Cases with Hepatitis or Concomitant Biliary Duct Infection as Cause. According to Alfred A. Strauss, Siegfried F. Strauss, Arthur H. Schwartz, William J. Tannenbaum, David D. Kram and

Walter W Masur (Chicago) some patients with acute or subacute hepatitis and jaundice who do not improve with medical management should be treated by bile duct drainage These patients have in addition to hepatitis inflammation of the intrahepatic and extrahepatic bile ducts which obstructs bile flow at the papilla of Vater Hyperemia makes dissection and identification of the common bile duct difficult and bleeding from the area is usually heavy

Of 26 patients who had surgical bile duct drainage 4 were unrelieved of jaundice and died several months later The remaining 22 recovered completely are well and have normal liver function Some might have recovered without surgery but it was felt that the recovery rate could not have been attained with medical therapy alone All had had an adequate trial of medical treatment and were in poor condition before surgery some being semistuporous Liver function tests indicated extreme liver damage Of another 34 patients chronically jaundiced because of infection of the common bile duct and the papilla of Vater 1 died and 33 recovered following surgical drainage

Common bile duct drainage relieves intraductal and intrahepatic pressure in congenital atresia acute and subacute hepatitis and infections of the papilla and bile ducts In hepatitis drainage of the common bile duct interrupts a vicious circle consisting of obstruction of bile flow at the papilla of Vater increased intraductal pressure to which liver parenchyma is expo ed and further breakdown and necrosis of liver cells

• [Everyone who has seen long standing cases of hepatitis with jaund ce has wondered whether or not some obstruct ve mechanism in the common duct perhaps an accumulation of mucus cellular detritus and bilirubin granules contributes to the jaund ce that never seems to end. On rare occasions this susp cion is heightened when a pat ent of this type suddenly seems to become less jaundiced after surgical drainage of the common duct or merely nonsurgical duodenal drainage If such cases exist it would be n ce to know by what criteria they might be selected for surgery Unfortunately the cases reported by Dr Strauss and his associates are not clearly defined and appear to comprise a variety of disorders Without clearer definition of underlying mechanisms hepatic pathology and rationale wholesale surgical intervention in patients with chronic and subacute hepatit s would it is to be feared represent a regression to the days when such procedures—and postoperative liver deaths —were all too common. —Ed.]

(7) *J A M A. 159 739 743 O t 2 1955*

Biliary Cirrhosis Differential Features of Five Types are reviewed by H Edward MacMahon[8] (Tufts College) The commonest type obstructive or cholestatic cirrhosis is induced by prolonged obstruction of a major hepatic or biliary bile duct The striking feature is centrolobular bile stasis In the portal areas interlobular bile ducts are conspicuous and a low grade chronic inflammatory reaction eventually leading to cirrhosis is present Cholestatic cirrhosis is usually caused by such choledochal lesions as stones chronic inflammations postoperative scars neoplasms and occasionally duodenitis and duodenal diverticula near the ampulla

A much less common type cholangitic biliary cirrhosis is characterized by inflammatory proliferation of new cholangioles Comparatively little bile is retained within the lobules Early in the disease it may be concentrated in the centers of the lobules but later quantity and distribution vary In chronic and healed stages periductal fibrosis and disappearance of interlobular ducts may occur In the precirrhotic phase the lesion is one of early cholangitic and cholangiolitic hepatitis Enterococci or coliform bacteria may at times be seen within the lumens of terminal cholangioles In cases apparently of bacterial origin a chronic or healed inflammation involves the extrahepatic biliary tract The large hepatic or common ducts are usually not obstructed The fact that biliary concretions are frequently found in the gallbladder or cystic duct and sometimes in the common duct has led to the hypothesis that some obstruction even though incomplete and temporary is an important factor Occasionally a similar type of disease co exists throughout the small pancreatic ducts

A third much less common type is pericholangiolitic biliary cirrhosis Histologically there is low grade chronic proliferative inflammation around the junction ducts and terminal cholangioles The granulation extends into the bordering parenchyma blocking the sinuses and separating rows of liver cells from one another and from the intact lobule The terminal cholangioles are only slightly proliferated Cellular exudate so conspicuous in the cholangitic type is relatively inconspicuous Pericholangiolitic biliary cirrhosis results from low grade chronic proliferative pericholangiolitic hepatitis Scarring of the portal areas and disappearance of many

(8) Lab I t 4 243 261 July A g 1955

interlobular bile ducts probably account for the jaundice and bile stasis so outstanding in this disease The early stages may be associated with mild chronic jaundice hypercholesteremia a large spleen and cutaneous xanthomatosis symptoms and signs rarely seen in the first two types

A fourth uncommon type is acholangic biliary cirrhosis and occurs in children up to age 12 These patients have a congenital defect of the interlobular bile duct system The liver is enlarged and its surface smooth or finely granular Microscopically there are perilobular fibrosis preservation of the lobule bile stasis a mild inflammatory reaction with slight proliferation of connective tissue and absence from some or all of the portal areas of collecting interlobular bile ducts

The least common type is fibroxanthomatous biliary cirrhosis characterized by infiltration and proliferation of cholesterol laden histiocytes in all portal areas This disease is part of a systemic disease in which the liver like many other organs is involved in an abnormal deposition of lipids in histiocytic cells accompanied by a low grade chronic inflammatory reaction The greatest concentration is in and around the walls of the interlobular bile ducts and extends into the peripheral zones of the lobules

Two or more types may be present at the same time Infection of the terminal bile ducts may become superimposed on long standing bile stasis and cholestatic cirrhosis may be complicated by the cholangitic type

• [Although biliary cirrhosis of Dr MacMahon s cholangitic type is recognized as a complication of chronic extrahepatic biliary tract stasis and infection it is less common knowledge that such cirrhosis apparently related to bacterial infection and accompanied by a similar process in the pancreas may develop without obstruction of the common duct or may progress after successful removal of a common duct stone —Ed]

Ammonia Levels in Blood and Cerebrospinal Fluid William V McDermott Jr Raymond D Adams and Athol G Riddell[9] (Boston) measured the ammonia levels in the peripheral blood and cerebrospinal fluid in 14 patients undergoing surgery for portal hypertension or with known liver disease Controls were patients without liver disease who were undergoing surgery requiring spinal anesthesia

Previous studies have shown elevations in blood ammonia levels associated with meat intoxication in the Eck fistula

(9) Proc Soc Exper Biol & Med 88 380 383 March 1955

dog and with episodes of stupor after surgical portacaval shunts in man Gross disturbances in ammonia metabolism have been described in patients with liver disease and central nervous system symptoms Portacaval shunts may allow abnormal amounts of ammonia to pass into the peripheral blood from the intestinal tract but how this interferes with central nervous system metabolic function is unclear

In controls the peripheral blood ammonia levels were normal and no appreciable ammonia could be detected in the cerebrospinal fluid Thirteen of the patients had abnormally elevated ammonia levels in the peripheral blood Levels in the cerebrospinal fluid were correspondingly elevated although consistently lower than in the peripheral blood Correlation between ammonia levels in peripheral blood and those in cerebrospinal fluid was excellent

Presumably this abnormal ammonia is consistently diffusible into the cerebrospinal fluid It is not known whether the abnormal elevations in cerebrospinal fluid ammonia levels are the cause or result of abnormal brain physiology Most likely some of the neurologic symptoms attendant on severe liver disease or presence of Eck fistulas are directly due to the toxic effect of ammonia on the central nervous system

• [In evaluating articles dealing with blood ammonia levels it should be remembered that the technics of measuring this substance in the blood are still very controversial The methods usually used measure ammonia or an enzyme or a substance that produces ammonia Even the apparent presence of ammonia in blood subjected to analysis within 10 seconds of its withdrawal does not establish the fact that normal blood contain ammonia because ammonia may be liberated from the blood even during the process of carrying out the analysis —Ed]

Production of Impending Hepatic Coma by Carbonic Anhydrase Inhibitor Diamox® Leslie T Webster Jr and Charles S Davidson[1] (Harvard Med School) gave diamox® 500 mg every other day to 1 000 mg daily for 3 27 days to 12 alcoholic patients with cirrhosis All patients had fluid accumulation and received weighed diets containing less than 270 mg sodium and 66-75 Gm protein daily

The normal range of blood ammonia levels by the method used is 29 80 μg NH_3 N/100 ml Before diamox® the patients had levels ranging from 28 to 114 μg /100 ml only two determinations exceeded 100

During diamox® therapy four patients had confusion with or without tremor and eight did not The first four patients

(1) Proc. Soc Exper Biol & Med 91 731 Ja[nua]ry 1956

had chronic severe cirrhosis and three previously had had impending hepatic coma Average venou blood NH_3 N concentrations tended to rise above control levels and in two of the patients who became confu ed the increase was striking Average serum potassium concentrations decreased by 0 4 mEq or more Potassium chloride failed to prevent or alleviate impending coma

The nitrogen content of diamox® was not the source of increased blood NH_3 N because in cirrhosis the drug is almost completely excreted in the urine The pathogenesis of impending hepatic coma after diamox® is different from that induced by nitrogenous substances Diamox® may have a direct effect on brain metabolism

Treatment of Hepatic Coma with L-Glutamic Acid is reported by William V McDermott Jr Joan Wareham and Athol G Riddell (Boston) in 28 patients who had varying degrees of encephalopathy associated with disease of the liver or portal circulation Normal range of blood ammonia by the method used is 40 80 µg /100 ml whereas initial levels in patients ranged from 162 to 735 µg /100 ml One group of patients with acute spontaneous encephalopathy had no precipitating factor such as ingestion of protein ammonium chloride or urea diuretics or gastrointestinal hemorrhage In a second group of patients the central nervous system disturbance was precipitated by a nitrogen load suddenly added to the gastrointestinal tract Most had abnormal hepatic function tests but were in reasonable clinical condition without neurologic symptoms until the sudden precipitation of typical encephalopathy of liver disease A third group of patients was chronically confused without rapid progre sion to coma and without apparent spontaneous remissions or exacerbations

l Glutamic acid was administered as the sodium salt 25 Gm /1L of 5 or 10% dextrose in water intravenously The daily oral dose was 25 Gm powder mixed in a liquid medium Such a large amount of sodium (169 mEq) was not always well tolerated A mixture containing 129 mEq sodium and 40 mEq potassium for each 25 Gm glutamic salt was substituted

Patients who had acute spontaneous encephalopathy without a precipitating factor did not benefit from glutamic acid

(2) New England J Med 253 1093 110 Dec 2 1955

although two patients improved temporarily In patients with acute exogenous encephalopathy precipitated by one of the above factors and in patients with chronic encephalopathy a distinct improvement was noted in most Over half were restored to a completely normal neurologic status

Restricting protein intake to 50 70 Gm daily improved the clinical status of the third group but no patient was restored to normal by this means alone Glutamic acid orally restored normal mental status and reduced the blood ammonia level in six of eight cases

[Therapy must be evaluated not only in terms of ammonia levels and neurologic status but also in terms of ultimate benefit to the patient Of the 14 patients with acute exogenous encephalopathy regarded as improved by l glutamic acid, 10 died within hours to days!—Ed.]

Effect of Sodium Glutamate on Hepatic Coma was studied by Leslie T Webster Jr and Charles S Davidson[3] (Harvard Med School) in 11 cirrhotic patients who were treated on one or more occasions for coma spontaneous impending coma or impending coma induced by ammonium salts

l Glutamic acid was given as sodium glutamate commercially prepared or prepared as follows 20 Gm l glutamic acid was neutralized with 20% sodium hydroxide to pH 7 4-7 8 and made up to a volume of 300 1 000 ml with sterile 5% glucose in distilled water This mixture containing about 23 Gm sodium glutamate was given intravenously during 3-4 hours in the afternoon to eight patients three received 103 355 Gm continuously over 17 93 hours Reactions were anorexia and vomiting controlled by slowing the rate of infusion

Two of the first eight patients one receiving glutamate on three separate occasions and the other on four consecutive days were comatose Neither demonstrated any consistent change in mental status tremor or plasma ammonia nitrogen (NH_3 N) levels In the impending coma group a single glutamate infusion was given on four occasions an infusion on two successive days was given three times and three infusions at daily intervals were given once In three instances the patient became worse and died slight improvement occurred three times and no change was found once Tremor remained the same or decreased in all and plasma NH_3 N rose in two remaining essentially unchanged in the others

One patient in whom impending coma was induced by oral

(3) J Clin Invest 35 191 199 February 1956

ammonium salts exhibited no change in confusion or tremor although plasma NH_3 N levels fell slightly after glutamate infusion The other patient became more confused and tremor was accentuated despite two consecutive daily infusions of glutamate Later glutamate given before and during administration of di ammonium citrate failed to prevent onset and exacerbation of impending coma or accentuation of tremor

The three patients who received more than 23 Gm glutamate daily had a temporary remission of coma In one of these who received 355 Gm sodium glutamate over 93 hours blood NH_3 N dropped from 2 6 µg /ml to normal except for two slightly elevated levels (1 5 µg /ml) 22 and 19 hours before death The other two patients also died one while receiving glutamate and the other five days after its discontinuance Blood NH_3 N concentrations were kept at or close to normal in all three patients The main complication of administering these large quantities of sodium glutamate was the development of hypokalemic alkalosis

Fetor Hepaticus was studied in the urine of a patient with massive hepatic necrosis by F Challenger and J M Walshe[4] (Univ of Leeds)

Woman 45 was hospitalized with jaundice and in light coma There was six weeks history of anorexia nausea and diarrhea Her urine had a strong fetor similar to that of the breath but more offensive The smell of the urine suggested an alkyl mercaptan alkyl sulfide or dialkyl disulfide or possibly all three By chemical identification the urine was found to contain methylmercaptan as the principal compound producing the odor and a smaller amount of dimethyl disulfide perhaps from oxidation of the methylmercaptan after the urine was passed No dimethyl sulfide was found

As in so many patients with severe liver disease the plasma methionine level was high This suggests that the mercaptan may have come from hydrolytic or reductive fission of the sulfur carbon bond in the methionine Normally methionine is a source of cysteine and of labile methyl groups for choline epinephrine creatine carnosine and N methylnicotinamide Otherwise its fate is in incorporation into proteins Many of the transmethylations occur in the liver In severe liver disease this action may be inhibited and methionine accumulates in the plasma Fission of the sulfur carbon link and methylmercaptan formation may then be an alternative pathway for excess methionine

(4) La et 1 1239 1 43 J 18 1955

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(3) J Cl I est 35 191 199 F brua y 1956

duct Mechanical defects irritating or obstructing the bile ducts were present in 40 patients (33%) The most common lesion was a persistent cystic duct stump observed in 20 patients In four of them the stumps contained calculi and in one the stump contracted as a gallbladder might after a fat meal In 11 patients calculi were lodged in extrahepatic ducts and in 10 the calculi were seen by cholangiograms 8 of these patients had no jaundice With 7 mm used as the upper limit of normal marked dilatation was noted in 9 of the 10 common bile ducts containing stones In 29 patients (24%) the only recorded abnormality was dilatation of the duct The relation between duct size and time lapse since cholecystectomy was not constant It should theoretically be possible to deduce the degree of bile stasis by determining the length of time it takes for the dye to appear in the duodenum after injection intravenously but this criterion appears unreliable

In 46 asymptomatic patients (42 women) the common bile duct was outlined in 44 Every type of duct lesion (including stones) observed in patients with symptoms was also seen in this group The incidence of demonstrable duct disorders was the same in both series and cystic duct remnants were almost twice as frequent in the control group Stones in the common bile duct were noted in two asymptomatic patients

Intravenous cholangiograms showed almost constant common duct dilatation after cholecystectomy in patients with and without symptoms The problem of biliary dyskinesia is still unsolved There was no evidence of increased bile stasis in the common duct of symptomatic patients compared to patients without symptoms In both groups the mean duct diameter was 9 mm Greatest dilatation was caused by calculi

Intravenous cholangiography efficiently demonstrates possible causes of recurrent symptoms after cholecystectomy but may not show the real cause of the complaints It is no substitute for sound clinical judgment

• [Most of the many articles on intravenous cholangiography describe the procedure and its findings but few have provided the objective and controlled evaluation performed by the Cornell group One additional use for the procedure suggested by P H Jordan Jr (Surg Gynec & Obst 10? ?18 1956) is in the d fie ent al diagnosis of the acute abdomen if the bile ducts are demonstrated but the gallbladder fails to fill in a patient suffering from an acute abdomen the diagnosis of acute cholecystitis must be suspected strongly —Ed]

Methylmercaptan has a more offensive odor than is commonly associated with classic fetor hepaticus It is relatively soluble and the urine would be the natural route of excretion The odor of fetor hepaticus is probably due to a mixture of dimethyl disulfide dimethyl sulfide and methylmercaptan The proportions of each may vary in different patients which may explain the differences in smell described by various observers

Little is known of the pharmacology of methylmercaptan dimethyl disulfide or dimethyl sulfide By analogy with closely related compounds they may well be toxic

• [Attempts to identify the chemical responsible for f tor hepaticus continue but to date the chemist s test tube has been no more consistent in his identification than the clinician s nose Methylmercaptan incidentally is alleged to be responsible for the urinary odor so prominent after asparagus has been eaten. According to your editor s nose post asparagus urine smell and hepatic fetor have little in common —Ed]

GALLBLADDER AND PANCREAS

Intravenous Cholangiography in Postcholecystectomy Syndrome According to John L McClenahan John A Evans and Paul W Braunstein (Cornell Univ) the term postcholecystectomy syndrome is ambiguous It is better described as recurrent biliary tract syndrome The condition has been attributed to mechanical irritation or obstruction of the common bile duct by stone or cystic duct remnant or functional spasm and in co ordination of the sphincter of Oddi

The authors studied 121 patients (100 women) with symptoms Each received a full dose of 40 cc of 20% solution of sodium iodipamide (cholografin®) injected intravenously The common bile duct was adequately seen in *87%* Preliminary skin testing was of little value in predicting toxic systemic reaction to the drug The results were inconclusive regarding pancreatitis—the common bile ducts were of normal diameter in three patients dilated in two and invisible in two of seven patients with chronic and recurrent pancreatitis None of the *patients had characteristic tapering constric*tion or displacement of the lower end of the common bile

(5) J A M A 159 1353 1357 Dec 3 1955

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(5) J A M A 159 1353 1357 Dec 3 1955

surface In a third patient the films showed good filling of intrahepatic ducts but the common hepatic was only partly filled and neither the gallbladder nor the common bile duct was visualized This led to erroneous diagnosis because not enough bile was aspirated before injection of iodopyracet Operation revealed pancreatic carcinoma with obstruction at the ampulla of Vater In another patient the first cholangio



Fig 98 (Cou t sy of K d1 H A AMA Ar h Su g 7 6 268 F b ry 1956)

grams were unsatisfactory because the patient moved but re injection of contrast medium showed a block in the common bile duct diagnosed as carcinoma of the common hepatic duct confirmed at laparotomy and autopsy In two patients chol angiography was carried out without incident revealing pa tency of a previous choledochojejunal anastomosis in one and an impacted stone at the ampulla of Vater later removed in the other

• [Such technics although still in the exploratory stage, are being at tempted with increasing frequency in France Spain and Latin America. An epigastric approach to the left hepatic lobe is preferred by some for the reason that large biliary channels in this area are more accessible

Percutaneous Transhepatic Cholangiography is reported in six cases by Henry A Kidd[6] (London) In jaundice and liver failure preoperative visualization of hepatic and biliary ducts is unsatisfactory with intravenous radiopaque medium (cholografin®) In such cases iodopyracet diodrast® introduced into the hepatic ducts by a needle passed through the skin and liver shows the site and nature of the obstruction Pressure in the bile ducts can also be recorded and bile taken for chemical and bacteriologic tests

TECHNIC —The patient lies on the x ray table and a subcutaneous procaine wheal is made in the skin just below the costal margin at the junction of the outer and middle third of a line joining the midline to the lateral border of the abdominal wall Subcutaneous fat muscles and fascia are infiltrated and a needle 15 cm long and 1 mm in diameter is introduced at an angle of 45 degrees to the horizontal plane and 15 degrees to the inner side of the vertical plane The patient is instructed to breathe as shallowly as possible and not to cough The needle is pushed on upward and slightly internally for about 4 in (10 cm) depending on thickness of the abdominal wall Even though blood is aspirated the needle should be pushed its whole length (Fig 98) Bile is usually aspirated after about 12 cm has been inserted and can be collected for desired tests When pressure is high 30 cc or more bile should be aspirated 18 cc of 50% iodopyracet is then injected and anteroposterior and lateral x rays are taken

The patient often experiences pain when the needle enters the capsule of the liver and should be warned of this Use of a narrow gauge needle that bends easily is important No trouble has arisen from intrahepatic or abdominal hemorrhage If bile cannot be aspirated during introduction or withdrawal of needle the needle should be reinserted in a slightly different place If bile is aspirated after the needle is inserted a short distance and the gallbladder is thought to have been punctured as much bile as possible should be aspirated and operation should be performed immediately

Among six patients the gallbladder was punctured in two in one of whom operation a few hours later showed leakage of bile from the gallbladder In the other when bile was aspirated at 7 cm 40 cc bile was aspirated and 8 cc iodopyracet injected The needle was pushed into the liver another 5 cm and 18 cc dye was injected Films outlined the whole biliary tract and showed cholelithiasis and one stone in the common bile duct Operation showed no bile leakage because the needle has transfixed the gallbladder on its hepatic

(6) A M A Arch S g 72 6 68 F b y 1956

not determined its color was noted The darker content apparently contained higher tetracycline concentrations although no significant relation between bilirubin and tetracycline elimination is known to exist In one case of carcinoma of the head of the pancreas with compression of the choledochal duct a nearly colorless duodenal juice had a low concentration of tetracycline

In normal persons the highest concentration of tetracycline in the duodenal secretion (liver bile) of three was higher than the concomitant blood level In patients with biliary tract disease the concentration of tetracycline in liver bile was always 2 12 times higher than that in the blood and exceeded therapeutic levels

• [It is generally believed that antibiotic concentration in bile is reduced when biliary secretion is impaired by liver di ease or obstruction of th extrahepatic biliary passages It is therefore unfortunate that measurements of liver function and of bile flow were not made in the patients who seemed to have a high biliary output of tetracycline in the face of hepatobiliary disease —Ed.]

Cystic Duct Remnant Sequela of Incomplete Cholecystectomy Frank Glenn and George Johnson Jr[8] (New York Hosp Cornell Med Center) have operated on and found a cystic duct remnant in 35 patients whose symptoms persisted or recurred after cholecystectomy The term postcholecystectomy syndrome is unfortunate because the pattern of symptoms following cholecystectomy is not regular The symptoms which persist are usually due to a condition other than cholelithiasis that was unrecognized or not evaluated before surgery Recurrent symptoms are usually due to an incomplete operation in which stones or a remnant of the gallbladder or cystic duct have remained The appearance of new symptoms suggests injury to the common duct

Pain is the outstanding symptom of cystic duct remnant In 74% the pain was severe and usually colicky Jaundice was present in 55% A long lag interval frequently occurred between cholecystectomy and development of symptoms the average interval was 3 8 years In a series collected from the literature the average was 4 3 years

Symptoms of cystic duct remnant are not pathognomonic Any patient who has had a cholecystectomy and complains of severe recurrent right upper quadrant or epigastric pain should be suspected of having a cystic duct remnant Symp

(8) S g Gy ec & Ob t 101 331 345 S pt mbe 1955

Peritoneoscopic control as is used by Royer for transcutaneous puncture of the gallbladder may increase the safety of the procedure —Ed.]

Studies on Elimination of Tetracycline in Bile in 24 subjects are reported by E Rissel H Schnack and F Wewalka[7] (Univ of Vienna)

METHOD —A duodenal tube was introduced under x ray control in fasting patients After bile flow began 20 cc of 40% $MgSO_4$ was instilled and duodenal contents collected for 45 minutes and discarded. Then 250 mg tetracycline in 100 cc of 5% dextrose was given intravenously over 10 minutes Outflowing duodenal contents (C bile) was collected in sterile tubes changed at 15 30 60 90 120 and 180 minutes Tubes were refrigerated and tests for tetracycline content made by the Dornbush and Pelcalk method In all patients blood tetracycline was determined 30 60 and 120 minutes after injection

In six normal persons the highest duodenal concentration of tetracycline was about 7 6 µg/cc after 1½ 2 hours There was no significant elimination during the first 30 minutes Average excretion (three hours) varied greatly in different persons (0 54 2 66 µg/cc average 0 95 µg/cc.) This concentration corresponds to a useful therapeutic level in bile

Two patients had chronic recurring cholangitis with subicterus and a state bordering on secondary biliary cirrhosis Concentration of tetracycline in the duodenal drainage rose to 5 and 17 4 µg/cc and total three hour excretion to 1 247 7 and 1 449 9 µg In both biligrafin was eliminated not by the liver but by the kidneys In five cholecystectomized patients with cholangitis the highest concentration of tetracycline was 7 6-44 µg/cc total elimination 835 1 891 µg with three hour average of 5 88 16 86 µg/cc (11 times normal) In these patients the highest concentration of tetracycline in the duodenal secretion was reached in 60 120 minutes

In three of seven patients with liver disease (one had steatosis with beginning cirrhosis another acute serum hepatitis and the third alcoholic cirrhosis) the concentration of tetracycline was higher than normal (over 10 µg/cc) Three patients with receding hepatitis reacted the same as normal subjects tetracycline elimination was 0 68 2 63 µg Average values in these cases of liver disease were highest concentration 8 3 µg total excretion 788 µg and mean tetracycline content/cc 3 9 µg

Although the bilirubin content of the duodenal content was

(7) Wien kl W h sch 67 83 839 O t 28 1955

tomy the gallbladder appeared normal on the serosal surface and the polyps could not be palpated through the gallbladder wall The gallbladders contained polyps due to focal cholesterosis

Papilloma and sometimes adenoma are words used to identify similar lesions in surgery By definition papilloma must show true hyperplasia of the epithelium and adenoma is a neoplasm composed of glandular tructures The epithelium of these gallbladder lesions is not hyperplastic and the stromal and epithelial growth is normal A more accurate term to describe the lesion is polyp of the gallbladder Polyp implies a benign lesion without suggestion of potential malignancy

The cause of gallbladder polyps is uncertain but the presence of lipoid material in the stroma suggests a metabolic disturbance They have occurred in gallbladders with chronic cholecystitis with and without stones as well as in gallbladders otherwise normal The diagnosis can be made by oral cholecystogram The polyps are discrete radiolucent areas that do not change position in multiple views and occur primarily in the midportion of the gallbladder

Cholecystectomy is usually advised on the presumption that the lesions are premalignant and may cause symptoms These tenets are doubtful Oral cholecystography should be repeated to determine changes in the polyps If the polyps or associated biliary disease changes cholecystectomy is indicated if the polyps remain unchanged in x ray further observation is justifiable

• [Polyp is a good example of a word that ha come to influence thinking by the power of what it suggests So much has been written concerning potential malignant degeneration of polyps in the gastrointestinal tract that the very hint of polyp in the gallbladder dispatches the patient whether symptomatic or not to the operating room This article emphasizes that such action is meddle ome the vast majority of radiologically detected gallbladder polyps are not of the type that can be considered premal gnant —Ed]

Hemocholecyst Following Ruptured Aneurysm of Portal Vein Report of a Case is presented by Raymond Barzilai and Martin S Kleckner Jr [1] (Tulane Univ)

Woman 21 who had had hepatitis during early childhood was examined after a massive gastrointestinal hemorrhage diagnosis was postnecrotic cirrhosis splenomegaly e ophageal varices and pancytopenia Splenectomy did not improve hematologic findings but portal venous pressure and size of esophageal varices decreased Ten months

(1) A M A. A h Su g 72 725 7 7 April 1956

toms of cystic duct remnant may be difficult or impossible to differentiate from those of common duct stone The high incidence of jaundice is difficult to explain Seven patients in whom no stone was found may have passed the stone before surgery Common duct stones found in the remaining 12 patients with jaundice may have been formed in the cystic and then passed into the common duct causing obstructive jaundice Of 35 patients in this series 10 and of 76 in a collected series of patients 17 had stones in the cystic duct remnant a total of 24% Over half the patients had stones in either the cystic or common duct The common duct was not explored in nine patients but the presence of a cystic duct remnant is an indication for choledochotomy

Intravenous cholangiograms were done in four patients in this series in two the cystic duct was not visualized Twenty seven patients were followed adequately and 19 (70%) were considered well Five continued to have symptoms none incapacitating Three patients died

If cystic remnant is suspected a careful thorough evaluation is indicated Once the diagnosis is established surgery should not be withheld unless contraindicated The general lack of understanding of these symptoms is suggested by the length of time between the development of symptoms and definitive therapy A cystic duct remnant may cause symptoms but may exist without pathologic changes or symptoms It should be considered as only one of the possible explanations for persistent or recurrent symptoms after cholecystectomy

• [Analysis of these 35 carefully described cases reveals that 25 had jaundice calculi in the cystic duct remnant, choledocholithiasis or a combination of these disorders This leaves 10 with no other apparent biliary tract disorder except a cystic duct remnant Following surgery three of these still had symptoms one was lost and six are well although the follow up period in five of these does not exceed two years The unavoidable question thus arises Does the mere presence of a cystic duct stump uncomplicated by stones inflammation or stricture cause symptoms and if so how? Do not Dr Glenn s colleagues in the X ray Department find the incidence of cystic duct stumps in patients with postcholecystectomy complaints 16 5% and in an asymptomatic control group 28%? See also article by McClenahan *et al* this YEAR BOOK p 596 —Ed]

Polyps of Gallbladder James W Martin[9] (Sacramento) presents two cases Cholecystograms showed a normally functioning gallbladder with shadows of diminished density that did not shift with the patient s position At cholecystec

(9) Sta f d M B ll 13 443-446 A g t 1955

ture of an aneurysm of the portal vein into the common hepatic duct has not been described previously as producing hemocholecyst Thus Courvoisier s law was mimicked by a hemocholecyst in a patient with jaundice Inflation and deflation of the gastric part of the pneumatic esophagogastric balloon was as ociated with increase or decrease re pectively in size of the hemocholecyst

Role of Pancreatic Juice in Cholesterol Absorption was studied by H H Hernandez I L Chaikoff and J Y Kiyasu (Univ of California) since previous experiments had suggested that the more rapid absorption of cholesterol compared to epicholesterol is related to esterification in the intestinal wall In male rats of the Long Evans strain a 0 5 mm polyethylene tube was inserted into the common duct at its junction with the duodenum to drain off both bile and pancreatic juice Through a second cannula in the duodenum bile pancreatic juice or both substances obtained from donor rats was dripped directly into the duodenum

The rats were given C^{14} cholesterol by stomach and absorption studied by measuring C^{14} in thoracic duct lymph Without bile cholesterol was not absorbed Without pancreatic juice cholesterol absorption took place at much reduced rates With both substances cholesterol absorption proceeded normally

Test rats receiving only bile were killed at various times after the administration of pancreatic juice was stopped homogenates of the duodenums prepared and the capacity of the e homogenates to esterify cholesterol measured The duodenum retained the ability to esterify cholesterol for some time after pancreatic juice was excluded but within 24 hours the homogenates had lost most of this ability

These studies showed that pancreatic juice is required for cholesterol to be absorbed E terification of cholesterol by duodenal homogenates depends on the presence of pancreatic juice in the inte tinal tract A factor in pancreatic juice which activates cholesterol estera e or cholesterol estera e itself may be responsible A highly purified preparation of cholesterol esterase did not require any cofactor other than purified sodium taurocholate

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(1) Am J Phy 1 182 523 5 6 J n 1955

later she was rehospitalized because of severe substernal pain jaundice light colored stools dark urine and weakness which had followed an acute upper respiratory infection Examination also disclosed generalized pruritus spider angioma palmar erythema ecchymoses pedal edema and dehydration The liver was *not palpable* Massive hematemesis required pneumatic esophagogastric tamponade and several blood transfusions Cholecystostomy was done after appearance of a firm globular mass in the right subcostal area and clotted blood was evacuated from the gallbladder Postoperatively blood drained con-

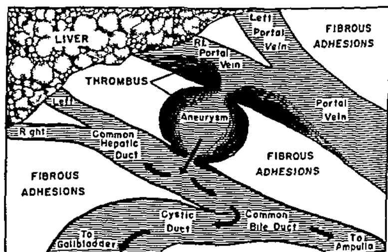


Fig 99 —Rep es tat on of p tm t m ob rvat s sh wing port l cur ysm ts uptu to th ommon hepat du t a d elat on h p to r d ng structure (C rt sy f Ba la R d Kl kn M S J A M A A h Sug 7 725 727 April 1956)

tinuously from the tube and melena persisted until her death a week later

At autopsy the distended gallbladder projecting 10 cm below the liver contained about 100 cc blood The entire hepatic and common bile duct systems contained blood An extensive network of collateral veins surrounded the hepatobiliary system The portal vein was dilated about 3 cm and a recent thrombus in the right branch partially *occluded the lumen Near the middle third of the thrombus* the wall of the vein had a saccular aneurysm about 2 cm in diameter containing clotted blood and communicating with the common hepatic duct about 1 cm above the junction of the cystic duct (Fig 99) The common bile duct was 2 cm in diameter Pathologic diagnosis was postnecrotic cirrhosis *esophageal varices aneurysm of portal vein with rupture* into common hepatic duct intracholedochal hemorrhage and hemocholecyst

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• [The physiologic implications are fundamental pancreatic enzyme may promote absorption not only by splitting lipids in the intestinal lumen

(2) Am J Phy 1 181 523 526 J 1955

later she was rehospitalized because of severe substernal pain jaundice light colored stools dark urine and weakness which had followed an acute upper *respiratory infection Examination also disclosed* generalized pruritus spider angioma palmar erythema ecchymoses pedal edema and dehydration The liver was not palpable Massive hematemesis required pneumatic esophagogastric tamponade and several blood transfusions Cholecystostomy was done after appearance of a firm globular mass in the right subcostal area and clotted blood was evacuated from the gallbladder *Postoperatively blood* drained con

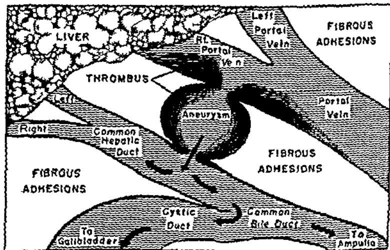


Fig 99—R presentat on of po tmortem b rvat ons h wing portal n neur ysm ts ruptu nt th ommon h p t c duct nd lat nsh p t sur d g structure (C urt y f D) R and Kleckn M S J A M A A h S rg 72 725 727 April 1956)

tinuously from the tube and melena persisted until her death a week later

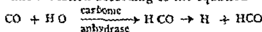
At autopsy the distended gallbladder projecting 10 cm below the liver *contained about 100 cc blood The entire* hepatic and common bile duct systems contained blood An extensive network of collateral veins surrounded *the hepatobiliary system* The portal vein was dilated about *3 cm and a recent thrombus in the right* branch partially occluded the lumen Near the middle third of the thrombus the wall of the vein had a saccular aneurysm about 2 cm in diameter containing clotted blood *and communicating with the common* hepatic duct about 1 cm above the junction of the cystic duct (Fig 99) The common bile duct was 2 cm in diameter Pathologic diagnosis was post necrotic cirrhosis *esophageal* varices aneurysm of *portal* vein with rupture into common hepatic duct intracholedochal hemorrhage and hemocholecyst

Massive *hemorrhage into the biliary tract following* rup

out pancreatic disease (Fig 100) With increasing dosage the volume response to secretin progressively diminished and at 80 mg /kg or more the decrease was sometimes more than 75% Total pancreatic secretion was less in patients with pancreatitis since the capacity of the pancreas was less but results paralleled those in patients without pancreatic disease

Data on total bicarbonate secretion showed that diamox® suppresses the basal rate of bicarbonate elaboration by the pancreas and inhibits the bicarbonate response to secretin Reduced bicarbonate secretion is probably due to two factors decreased secretion of fluid and to a lesser degree decreased ability to secrete high concentrations of bicarbonate Total amylase secretion was decreased after diamox® probably also because of diminished fluid formation

Neither secretin nor diamox® affected sodium or potassium concentrations of the collections Chloride concentrations varied inversely with bicarbonate concentrations Some serum bicarbonate ion perhaps up to 20% can be utilized by the pancreas in secretion of bicarbonate The remainder is derived from intracellular oxidation Carbonic anhydrase enhances this oxidation according to the equation



$$CO + HO \xrightarrow[\text{anhydrase}]{\text{carbonic}} HCO \rightarrow H + HCO$$

Carbonic anhydrase inhibitor presumably acts in this reaction

Stimulation of pancreatic flow by secretin is not dependent on a carbonic anhydrase activity of its own and is not related to catalysis of human carbonic anhydrase activity Perhaps secretin inhibits an intracellular carbonic anhydrase inhibitor Diamox® may be useful in treatment of acute and chronic pancreatitis

* [According to theory diamox® prevents carbonic anhydrase from making bicarbonate available for pancreatic secretion Yet diamox® does not affect the concentration of bicarbonate in pancreatic juice it merely decreases total bicarbonate output by decreasing volume output This is hard to interpret unless it is assumed that bicarbonate secretion is the sole determinant of fluid output.—Ed]

Prevention of Pancreatic Fat Necrosis IV Experiments with Carbonic Anhydrase Inhibitor (Diamox®) H L Popper J Sporn M Levinson and H Necheles[4] (Michael Reese Hosp) aseptically excised the pancreatic duct from the duodenum in 21 dogs Diamox® 9 50 mg /kg daily was

(4) Am J Phy 1 181 191 19 Ap 1 1955

but also by combining them (i e esterification) within the intestinal mucosa —Ed]

Effect of Carbonic Anhydrase Inhibitor Diamox® on Human Pancreatic Secretion Implications on Mechanism of Pancreatic Secretion David A Dreiling Henry D Janowitz and Mark Halpern[3] (Mount Sinai Hosp, New York) collected gastric and duodenal drainage simultaneously from 4 patients with chronic pancreatitis and 14 without pancreatic

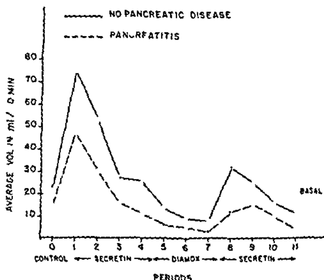


Fig 100—Average period volumes after secretin administration before and after diamox® infusion (Courtesy of Dreiling D A et al Gastroenterology 9 262-279 August 1955)

disease before and after the pancreas was stimulated by 1 clinical unit of secretin/kg body weight given intravenously The tests were then repeated after intravenous administration of diamox® The dose used 10 121 mg/kg was much higher than that used orally for congestive failure but no patient had side reactions such as paresthesia drowsiness disorientation or changes in pulse blood pressure or respirations

Control observations without diamox® showed that values for volume and bicarbonate did not vary by more than ±15% on successive secretin tests in the same subject Volume changes induced by diamox® were the same with and with

(3) Gastroenterology 29 26 279 August 1955

est and most frequent change In more advanced lesions acinar cells were flattened and of atypical appearance Mild interstitial infiltration of lymphocytes and plasma cells was usually present In regions of fat necrosis there were often many polymorphonuclear leukocytes Diffuse spreading purulent or hemorrhagic pancreatitis was not observed

Characteristic peripancreatic fat necroses were found in 13 of 44 rabbits with pancreatic acinar lesions none was observed in animals with a normal pancreas Grossly the pancreas was generally normal in appearance but close inspection sometimes revealed minute flecks of opaque white fat necrosis to 4 mm in diameter in immediately adjacent adipose tissue

The livers of most cortisone treated animals were enlarged and liver cells contained large amounts of glycogen Liver necrosis was absent in 16 rabbits with pancreatic lesions but small areas of focal necrosis were seen in others

Of 36 cortisone treated rabbits with pancreatic lesions 34 had moderately or markedly elevated blood amylase levels Hypercholesterolemia produced by cholesterol feeding or triton injections did not significantly modify the pancreatic injury in cortisone treated rabbits However repeated large doses of cortisone alone caused grossly visible sustained neutral fat lipemia The degree of pancreatic injury was not directly proportional to the degree of the hyperlipemia in every instance but severe pancreatic lesions and high blood amylase were found most often when cortisone produced an unusually sharp rise in neutral fat levels without concomitant equal increase of cholesterol or phospholipid The findings are reminiscent of the relapsing pancreatitis described in patients with essential hyperlipemia

Pancreatic lesions in rabbits receiving cortisone are very similar to lesions in rats and dogs after ethione administration and in experimental pancreatitis produced by other means

• [These observations do not particularly support the exhibition of cortisone in the management of pancreatitis Acute pancreatitis incidentally occasionally develops in patients maintained on adrenocortical therapy for other diseases the precipitating lesion may be a penetrating gastric or duodenal ulcer —Ed.]

Clinical Features of Acute Inflammation of Pancreas Analysis of 94 Attacks in 78 Patients was made by H L Bockus M H Kalser J L A Roth A L Bogoch and G

given intravenously to 10 of the dogs on the day of surgery and postoperatively

Birnbaum and Hollander have reported that similar treatment in pancreatic fistula dogs caused marked reduction in volume output and bicarbonate concentration of secretin stimulated pancreatic secretion This was ascribed to inhibition of pancreatic carbonic anhydrase and interference with bicarbonate formation in the gland Apparently the inhibition lasted at least six hours and was unrelated to the dose of diamox® used

Of 11 control dogs in this experiment fat necrosis developed in 9 and was fatal in 8 with an average length of survival of 2 4 days Of the 10 dogs that received diamox® 8 had fat necrosis which was fatal in 7 with an average length of survival of 2 6 days The degree and extent of fat necrosis was approximately the same in both groups

Diamox® intravenously in repeated doses did not prevent fat necrosis and did not appreciably change the postoperative course If pancreatic secretion had been inhibited some diminution of fat necrosis and prolongation of survival should have been apparent

• [In comparing these results with those presented in the preceding abstract it must be understood that Popper and his associates used diamox® in doses of 9 50 mg /kg daily whereas Dreiling s group gave 10 120 mg /kg intravenously over one hour —Ed]

Pancreatic Lesions and Peripancreatic Fat Necrosis in Cortisone Treated Rabbits Harry H Stumpf Sigmund L Wilens and Cesar Somoza[5] (New York Univ) report histologic findings in pancreatic tissue from 53 rabbits that received cortisone intramuscularly for 21 81 days Some were given cortisone daily others had injections daily for two week periods with intervening two week rest periods Average daily dose was 3 8 Gm /kg Cortisone alone was given to 22 rabbits others had various supplements including 1% cholesterol 1 10% neutral fat (added to food) triton ACTH depo* heparin oxytetracycline protamine sulfate or methionine

Pancreatic acinar changes were found in 44 animals although lesions were very small in 17 Of 22 that received cortisone alone 19 had pancreatic lesions No comparable lesions were noted in 24 control rabbits Reduced basophilia of the basal portion of acinar cells in patchy areas was the earli

(5) Lab Inv t 5 4 235 M r Ap 1956

betes had been present in one before pancreatitis Serum amylase was persistently normal in 11% but most of these patients had been admitted several days after the onset of symptoms Since serum amylase rapidly returns to normal the determination may have been done too late to show elevation Nine patients who had normal amylase had increased lipase concentrations Two patients had normal concentrations of both amylase and lipase and both died of hemorrhagic pancreatitis Serum amylase was less than five times the average top normal value in 42% of the patients and greater than five times in 47% Serum lipase was normal in 13 patients

In 23 patients abdominal films were interpreted as normal

TABLE 2 —Disturbance of Glucose Metabolism

	No. P
Normal blood glucose*	57
Diabetes before attack	1
Transient *hyperglycemia*	17
Diabetes†	4
Diabetic glucose tolerance	3

* [illegible]
† [illegible]

23 showed localized ileus suggestive of pancreatitis and 4 had mechanical obstruction or generalized ileus Of 30 chest films taken 16 showed some pathology including elevation of the diaphragm pneumonitis linear atelectasis or hydrothorax

Cholecystograms were abnormal in all the patients whose pancreatitis was subsequently proved due to biliary tract disease In the alcohol group 12 of 14 cholecystograms taken 4-14 days after the acute attack were normal In two filling was not seen Pancreatic lithiasis was seen in six patients in the alcohol group and one in the biliary tract group

Of 12 patients explored within 48 hours of hospitalization 10 had a stormy postoperative course and 3 died Of the 82 treated medically 1 died—a chronic alcoholic hospitalized three weeks after onset of symptoms mortality rate was 1 3% Operation is contraindicated in the presence of acute pancreatitis

Acute pancreatitis of alcoholic etiology seems more severe the incidence of complications and recurrences higher and prognosis poorer than in pancreatitis due to other causes

Stein[6] (Univ of Pennsylvania) Patients were hospitalized with primary or recurrent acute pancreatitis between 1941 and 1954 The incidence of acute pancreatitis has been increasing in recent years—50% of the patients were hospitalized during the last two years of the study This increase is due in part to greater awareness of the disease and more frequent serum pancreatic enzyme determinations

Table 1 lists the causative factors in these patients Excessive alcohol intake or biliary tract disease was present in 86% The admission diagnosis was correct in 54 cases Most commonly biliary tract disease was mistaken for acute pancreatitis In 21% proved episodes of pancreatitis had occurred These were more frequent in the alcohol group than in the biliary tract group Many other patients had previously had pain similar to the pain at admission but less intense and of shorter duration Pain on admission was in the epigastrium in most patients and commonly radiated to the back

TABLE 1 —Etiology

	No Patients	Admissions
Alcohol*	31	41
Biliary tract disease	36	39
Surgical trauma	3	3
Allergy	1	1
Probably alcohol	2	3
Probably biliary tract disease	2	2
Unknown	3	5

* One patient had calculus in main pancreatic duct

Clinical icterus was noted in 20 patients of the group with biliary tract disease and in 1 of the alcohol group Abnormal pulmonary findings were described in 30% The most common finding was rales but a few had rhonchi tubular breath sounds or no breath sound One patient had a friction rub The signs were predominantly on the left side in the alcohol group and on the right in patients with biliary tract disease

White cell counts ranged from 5 000 to 30 000 cells/cm In 60% of patients with alcoholic etiology the leukocyte count was 10 000 or less Table 2 lists the results of blood glucose determinations which were abnormal in 25 patients Dia

(6) A M A Arch Int Med 96 308 321 September 1955

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Relapsing Pancreatitis with Pseudocyst of Pancreas and Enzyme Containing Pleural Effusion A case is reported by M H Kalser J L A Roth and H L Bockus[7] (Univ of Pennsylvania)

Woman 57 had primary acute pancreatitis 10 weeks before hospitalization Cholecystectomy revealed hydrops of the gallbladder and a solitary stone in the cystic duct with a large cyst in the region of the pancreas The cyst was ruptured during surgery In the four weeks postoperatively she lost 30 lb was anorectic and weak and had pain in the left chest aggravated by inspiration

Physical examination revealed an obese woman moderately ill Over the lower half of the posterior chest vocal fremitus was decreased breath sounds absent and percussion note dull The abdomen was distended and muscle guarding and tenderness were present in the left upper quadrant there was a large cystic mass in the left epigastrium

CONCENTRATION OF PANCREATIC ENZYMES

D	Serum		Pleural Effusion		Pseudocyst	
	Am	Lip†	Amyl	Lip†	Amyl	Lip†
1953						
N 5	525	2 5	1723	20 4	—	—
N 11	10 0	3 5	—	—	—	—
N 12‡	—	—	—	—	2467	44 0
N 16	60	0 8	592	5 6	—	—
Nov 24	47	0 7	—	—	1686	29 6
Dec 3§	5	—	—	—	83	2 70

Amylase expre d s mg /100 ml gluc e
†L p xpres ed a c N/ 0 N OH
‡F pl t on w th d n g f pseudocy t
§Dra n g f purul t ll t on

Pleural fluid was removed by thoracentesis Exploratory laparotomy revealed dense adhesions and a large cavity in the left upper quadrant oozing brownish black fluid An infradiaphragmatic collection of pus was later aspirated and more pleural fluid removed Abdominal drainage gradually stopped and the patient was discharged She continued to have intermittent episodes of epigastric distress and one of clinical jaundice Six months later a recurrent large mass was proved to be a pancreatic cyst and was internally drained by cyst jejunostomy

The table lists the concentrations of pancreatic enzymes in the body fluids Concentrations in the pseudocyst were in the range found in pancreatic juice and were lower in the pleural fluid and serum

Fluid from the pseudocyst was chocolate brown color and

(7) Gastroenterology 28 842 850 May 1955

from the pleural effusion was straw colored evidence against an actual anatomic fistula This was confirmed by the difference in enzyme concentrations and no communication was seen at surgery Enzymes probably entered the blood after absorption into the lymphatics and the pleural cavity by lymphatic vessels which traverse the diaphragm Enzymes in the blood originated in the pancreas the pancreatic cyst and the pleural fluid

• [The preceding two articles draw attention to the frequency and nature of the pulmonary pleural disorders that may attend pancreatitis They are sufficiently striking that at times cases of pancreatiti are erroneously treated for primary pulmonary d sease —Ed]

Eight Year Study of Pancreatitis and Sphincterotomy in 319 patients is reported by Henry Doubilet and John H Mulholland[8] (New York Univ) In pancreatitis there is spasm of the sphincter of Oddi with increasing resistance to the flow of bile and pancreatic juice and often distention of the biliary pancreatic duct system Calcification of the pancreas was present in 14 patients appearing suddenly in 2 after an acute attack

Accumulation of pancreatic juice in the retroperitoneal tissues was a common occurrence Seepage into the left side often formed large pseudocysts extending from sigmoid colon to subphrenic space Anterior extension between the leaves of the mesocolon sometimes obstructed the left transverse colon Occasionally a left perinephric abscess or acute renal inflammation with albumin casts and red cells in the urine occurred Pseudocysts were rare on the right side

Fluid loss required large amounts of water sodium potassium blood and plasma for replacement Psychotic excitement and hallucinations which occurred in 22 patients were related to low blood pota sium levels they were often misdiagnosed as delirium tremens The serum amylase was high in 118 cases Operative cholangiograms demonstrated a common passageway between bile and pancreatic ducts in 196 patients

During the acute phase threatment includes nasogastric suction anticholinergic drugs (atropine or pro banthine®) sedation with meperidine (demerol®) hydrochloride and phenobarbital sodium intramuscularly fluid and electrolytes to replace losses and antibiotics to prevent secondary growth of organisms in exudate or necrotic tissue The nasogastric

(8) J A M A 160 5 1 5 8 F b 18 1956

tube should be used for three days or until the serum amylase becomes normal Fat containing foods are contraindicated since they might cause a recurrent attack After recovery an elective sphincterotomy may be done

Of the 319 patients 91 had endocholedochal and 228 trans duodenal sphincterotomies The sphincter should be cut for a distance of only 6 10 mm to avoid interference with duo denal wall contraction which must be maintained to prevent duodenal reflux The gallbladder was present in 249 patients Nine patients had surgery for large pseudocysts three of whom also had true cysts by pancreatographic study After sectioning the sphincter the gallbladder cannot fill normally so it should be removed when sphincterotomy is done

Sphincterotomy abolished pain due to distention of the ducts and to reflux bile Reducing intraductal pressure cured the pseudocysts acute true cysts and pancreatic fistulas Dis ease progression was arrested and the pancreas regenerated within limits Reactions to pain emotion drugs or acid ap plied to the papilla—all present before surgery—were abol ished Ingestion of alcohol or fats still produced pancrea titis probably on a metabolic basis since it is unaffected by sphincterotomy vagotomy or gastric operations After sphincterotomy it is essential to watch the diet closely for at least 1 year and to offer encouragement when a setback due to dietary indiscretion occurs

• [Here the authors summarize their extensive experience with pan creatitis and its treatment The clinical information presented is in valuable The efficacy of sphincterotomy however is moot In their physiologic studies the authors have failed to measure intraperitoneal pressure concurrently with intracholedochal pressure Without such con trol it is impossible to determine whether or not a sudden increase in intraductal pressure such as is described in certain patients exposed to needle puncture is related to contraction of the sphincter of Oddi or as is more likely to fixation of the diaphragm with tensing of the abdomi nal muscles On the clinical side the reader gets the impression that sphincterotomy was often carried out after just one attack of pan creatitis Certainly the finding of calcification of the pancreas in only 34 of the 319 cases is less than is usually seen in chronic relapsing pancreatitis Finally the authors themselves did not find sphincterotomy too beneficial in patients who continued to drink alcohol Is it not possible one cannot help asking that many of the patients treated with sphincterotomy would have been equally well had nothing been done?—Ed]

METABOLISM



PHILIP K BONDY M.D

PART VI

METABOLISM

THE ADRENAL GLANDS

Stimulation of Release of Corticotropin from the Adenohypophysis by a Neurohypophysial Factor Murray Saffran A V Schally and B G Benfey[1] (Montreal) detected an ACTH releasing factor in the posterior pituitary extracts of rats distinct from the factors of vasopressin and oxytocin Anterior pituitary tissue was incubated with test substances and the ACTH released bioassayed

The ACTH releasing activity of the neurohypophysis does not require surviving tissue and can be demonstrated in a water extract of rat *neurohypophysis* Arterenol *increased* the release of ACTH from adenohypophysial tissue incubated with neurohypophyses Acetone powders of beef and hog posterior pituitaries contain an ACTH releasing factor Vasopressin and oxytocin prepared from beef posterior pituitaries had little ACTH releasing activity Vasopressin plus arterenol stimulated ACTH release but oxytocin had little activity with or without arterenol and after further purification vasopressin lost most of its activity

The neurohypophysis is an important link in the pituitary adrenal response to stress Arterenol (or epinephrine) acts synergistically with the ACTH releasing factor What controls the discharge of the ACTH releasing factor is unknown

The chemical nature of the ACTH releasing factor of the neurohypophysis is unknown It may be a peptide for it contaminates vasopressin but can be separated by paper chromatography It is distinct from vasopressin and oxytocin

ACTH Release by in Vitro Pituitary Effect of Pitressin® and Purified Arginine Vasopressin was studied by Roger Guillemin and Walter R Hearn[2] (Baylor Univ) The an

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(1) E docrı l gy 57 439 444 Oct b 1955
(2) P oc Soc Expe B l & M d 89 365 367 J l 1955

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Exper Biol & Med 89 36 36 July 195

terior lobes of rat pituitary were cultured in vitro After two days ACTH activity of the culture fluids was not significantly different whether the pituitary was cultured alone with vasopressin or with pitressin® No ACTH was secreted by isolated pituitary glands after more than two days in vitro and purified arginine vasopressin had no effect on the release of ACTH Only when incubated with commercial pitressin® was the ACTH activity increased after four days of culture Significant amounts of vasopressor activity were present after two and four days of incubation amounts up to 1 unit of vasopressor activity were not detrimental to the living cells of the culture

Posterior lobe activity is not necessary for release of ACTH by the in vitro pituitary Commercial pitressin® can increase ACTH release in vivo but the vasopressin probably is not responsible The ACTH hypophysotrope activity of pitressin® should be attributed to another of its constituents present as a contaminant and probably originating in the hypothalamus The presence of ACTH after four days of culture with repeated doses of pitressin® may have resulted from a cumulative effect of the activating factor This is especially significant since in the absence of activating factors ACTH activity is never found after two days of culture

• [These studies further extend our understanding of the control of ACTH release (see 1955 56 YEAR BOOK p 605) —Ed]

Effect of Thyrotropin on Adrenocortical Function J L Gabrilove and L J Soffer[3] (Mount Sinai Hosp New York) gave 25 50 mg (10 20 I U) thyrotropin in one or two daily injections for 6 21 days to two euthyroid subjects three with primary hypothyroidism and four with hypothyroidism secondary to hypopituitarism (Sheehan s syndrome)

In the subjects with intact thyroid or with secondary hypothyroidism thyrotropin caused a rise in BMR and serum protein bound iodine content In the subjects with hypothyroidism due to a primary defect or absence of the thyroid thyrotropin had no definite effect on the indexes of thyroid or adrenal function the adrenal cortex responded adequately to stimulation by corticotropin

In the euthyroid and hypopituitary subjects the increased thyroid activity was accompanied by a decrease in excretion of formaldehydogenic corticoids In the patients with hypo

(3) J Clin Endocrin 15 585 591 May 1955

pituitarism disappearance of these compounds from the urine was associated with acute adrenocortical insufficiency which required prompt and vigorous replacement therapy This precipitation of adrenal crisis suggests that physiologic need for adrenocortical hormones of the glycogenic corticoid type exceeds the capacity of the adrenal to produce them when the metabolic rate is increased In the patients with hypopituitarism and in one euthyroid subject the decrease in excretion of the formaldehydogenic corticoids was not associated with changes in excretion of neutral 17 ketosteroids These observations may explain the precipitation of adrenal crisis in patients with Sheehan s syndrome given thyrotropin or desiccated thyroid

• [These data should not be interpreted to mean that in hypopituitarism increased thyroid secretion is associated with decreased adrenal activity The urinary *formaldehydogenic steroid assay is subject to serious criticism* because of the presence of formaldehyde binding substances in certain urines Increased thyroid activity might alter the quantity of these substances in the urine thus producing spurious reduction of steroid excretion rates Moreover the urinary formaldehydogenic steroids represent only a small fraction of the total corticoids secreted by the adrenal over 80% of the adrenal corticosteroids are excreted in some other form The development of hypoadrenalism however implies either that decreased adrenal secretion occurred or as the authors suggest that an increased need for adrenal steroids developed which could not be satisfied because of absence of endogenous ACTH —Ed]

Serum Corticoids in Liver Disease were studied by R Klein C Papadatos J Fortunato Camilla Byers and A Puntereri[4] who measured both free and conjugated serum corticoids (acid hydrolyzable) in normal persons and in patients with liver cirrhosis The latter had had symptoms of this disease for over one year and were jaundiced at the time of the studies The measurements were made before and after ingestion of cortisone before and after receiving ACTH intravenously and before and after undergoing surgical procedures

The differences in conjugated serum corticoids between random pretreatment measurements in patients with liver disease and in normal persons were highly significant

Patients with advanced liver disease have a defect in the conjugation of exogenous and endogenous corticoid which apparently is related albeit crudely to degree of liver dysfunction If the patients with the mildest liver disease and the one who absorbed little if any cortisone are eliminated those

(4) J Clin Endocrinol 15 943 95 Aug t 1955

with liver disease had a higher peak level of free serum corticoid after a given dose of cortisone by mouth than did the normal subjects It is possible that the higher free corticoid levels in these patients were the result of less destruction of the hormone in the gastrointestinal tract or greater absorption or both However in patients with liver disease the rate of removal of intravenously administered hydrocortisone is slower than in normal persons

There is no evidence that conjugated serum corticoid exerts any metabolic effect The level of this corticoid rises in the presence of normal free corticoid during renal failure but *elsewhere it reflects the previous level of free corticoid*

Highly Potent Adrenal Cortical Steroids Structure and Biologic Activity George W Thorn Albert E Renold William I Morse Alan Goldfien and William J Reddy[5] (Harvard Med School) compared the physiologic activity of steroid derivatives and estimated the relative potentiation of organic as contrasted to the inorganic metabolic regulating potency of 9 α fluorohydrocortisone Δ 1 hydrocortisone and aldosterone using hydrocortisone as a point of reference The structural formulas are given in Figure 101

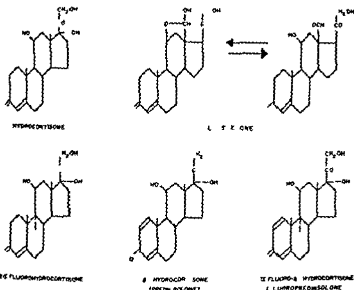
Fluorohydrocortisone is at least 50 times as active as hydrocortisone *in its electrolyte regulating* capacity and about 20 times as great in its organic regulating potency If hydrocortisone is assigned a sugar activity of 1 and a salt activity of 1 its sugar salt ratio is 1 Comparable values for fluorohydrocortisone then are 20 50 and a ratio of 0 4

The introduction of a double bond between carbon 1 and 2 of hydrocortisone resulted in Δ 1 hydrocortisone (prednisolone) a compound with enhanced anti inflammatory potency but unchanged sodium retaining activity The comparative effects of Δ 1 hydrocortisone and hydrocortisone are shown in Figure 102 The organic metabolic regulating *activity of* the Δ 1 compound was increased by a factor of 4 compared with hydrocortisone total nitrogen excretion was noticeably and persistently increased and increase in uric acid and true urinary glucose excretion occurred The organic metabolic regulating activity of Δ 1 hydrocortisone is increased over sodium retention a distinct therapeutic feature when an anti *inflammatory response is desirable* without the limiting factor of excessive sodium retention

(5) Ann Int Med 43 979 1000 November 1955

However Δ 1 hydrocortisone has definite sodium retaining activity about equal to that of hydrocortisone Using the same scale of 1 for hydrocortisone Δ 1 hydrocortisone may be assigned a sugar activity of 4 a salt activity of 1 and a sugar salt ratio of 4

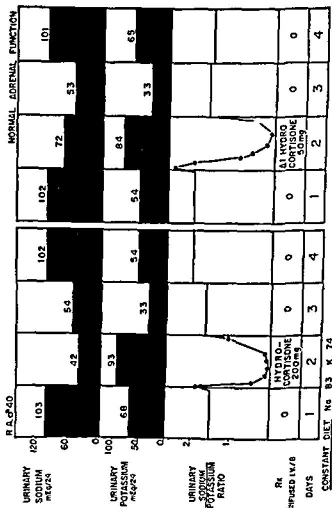
Compared with hydrocortisone the activity of Δ 1 fluoro



F g 101 —Struct l form l f steroids (Court y f Th eu G W et l A n I t Med 43 9 9 1000 N mbe 1955)

hydrocortisone is similar to that of fluorohydrocortisone The marked increase in both organic and inorganic regulating activity is offset because of the relatively greater potentiating salt retention The sugar salt ratio or therapeutic index was 0 4

Aldosterone has definite sodium retaining and potassium excreting activity The organic regulating effect has been difficult to evaluate because the marked eosinopenic effect is at variance with the hormone s negligible effect on other carbohydrate regulating mechanisms However aldosterone has been assigned a sugar activity of about 1 a alt activity of 50 or more and a sugar salt ratio or therapeutic index of 0 02



Anti inflammatory activity in general parallels carbohydrate activity and in most patients the steroids are used for their anti inflammatory activity For these patients the therapeutic index is more favorable for Δ 1 hydrocortisone and less favorable for 9 α fluorohydrocortisone In the treatment of Addison s disease the increased sodium retaining activity of 9 α fluorohydrocortisone would be par ly useful

When the diagnosis of Addison s disease depends on the steroid excretion in response to ACTH but the patient must be maintained on substitution therapy 9 α fluorohydrocortisone could be used in doses of 0 5 1 mg daily The urinary steroid metabolites from the administered fluorohydrocortisone are negligible

* [The availability of a variety of synthetic steroids offers the clinician the opportunity to adjust his therapy to the specific needs of the patient but to do this intelligently a clear understanding of the relative effectiveness of the various compounds is essential —Ed]

Clinical Application of Simplified Silber Porter Method for Determining Plasma 17 Hydroxycorticosteroids Eleanor Z Wallace Nicholas P Christy and Joseph W Jailer[6] (Columbia Univ Presbyterian Med Center) studied 50 normal subjects and 109 patients with miscellaneous non endocrine diseases renal disease nonadrenal endocrine disorders or adrenocortical disease including Cushing s syndrome adrenal insufficiency and congenital hyperplasia

In certain clinical situations plasma values for 17 hydroxycorticosteroid levels are more indicative of adrenal function than are urinary values In the circulation 17 hydroxycortisosteroid accounts for most of the adrenal cortical production and estimations of plasma levels should afford valid information about adrenocortical function

The range in 50 normal subjects was 4 32 μg /100 ml plasma with an average of 16±6 9 μg Most patients with nonendocrine diseases and patients with nonadrenal endocrine diseases had normal plasma 17 hydroxycorticosteroid levels Elevated levels were found in diabetic acidosis in 3 of 19 patients with renal disease and in 2 moribund patients None had clinical hyperadrenalism Patients with renal insufficiency had normal or elevated plasma corticoid levels in contrast with the abnormally low urinary 17 ketosteroid and corticoid values sometimes observed

In patients with Cushing s syndrome plasma levels ranged from 29 to 107 μg /100 ml Only 2 of 19 determinations were in the high normal range In two patients the elevated plasma corticosteroid levels more accurately reflected the adrenocortical status than did the normal urinary steroid excretion values After unilateral adrenalectomy despite bilateral adrenal hyperplasia plasma levels fell constantly unrelated to clinical status After bilateral adrenalec

(6) J Cl E doc 1 15 10 3 1088 S pt mb 1955

tomy in these patients correlation between fall in plasma corticosteroid levels and clinical improvement was closer

In patients with both primary and secondary adrenocortical hypofunction plasma corticosteroid levels were generally low though several patients in each category had normal values Testing the response to ACTH plasma gave a better index of adrenal insufficiency whether primary or secondary than any number of single plasma corticoid determinations In primary adrenal insufficiency values ranged from 0 to 21 µg /100 ml plasma In hypoadrenalism secondary to pituitary insufficiency values ranged from 0 to 12 µg

The Silber Porter technic for estimating plasma corticosteroid levels is accurate easily adapted to a general hospital laboratory and useful in distinguishing various clinical states It can be a routine diagnostic procedure as many as 15 patients being completely tested during a working day

Effect of Intravenously Administered ACTH on Plasma 17 21 Dihydroxy 20 Ketosteroids in Normal Individuals and in Patients with Disorders of Adrenal Cortex was investigated by Nicholas P Christy Eleanor Z Wallace and Joseph W Jailer[7] (Columbia Univ) They gave 25 mg ACTH intravenously over four hours to normal individuals to pregnant women and to patients with Addison s disease hypopituitarism Cushing s syndrome and congenital adrenal hyperplasia

Changes in plasma 17 hydroxycorticosteroid levels were rather constant in normal subjects No increase in plasma levels was encountered in patients with Addison s disease Subnormal rises were demonstrated in patients with hypopituitarism and congenital adrenal hyperplasia (Fig 103)

Groups showing an exaggerated plasma 17 hydroxycorticosteroid rise after ACTH were (1) patients with Cushing s syndrome due to bilateral adrenal hyperplasia and (2) normal women in the third trimester of pregnancy In Cushing s syndrome this excessive response occurred even after removal of one of the hyperplastic adrenal glands In two of the patients studied following bilateral subtotal adrenalectomy subnormal increases in plasma 17 hydroxycorticosteroids were noted after ACTH One patient with Cushing s syndrome due to adrenal carcinoma showed a plasma 17 hydroxycorticosteroid rise of much smaller magnitude than

(7) J Cl I t 34 899 906 J n 1955

that found in patients with hyperplasia Experience with adrenal adenomas has been too limited to permit a definite statement concerning the usefulness of testing the response to ACTH in distinguishing Cushing s syndrome of this eti

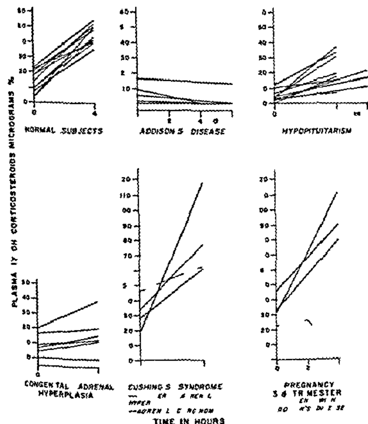


Fig 101—Effect f ACTH dm t 1 n n plasm 1 OH-c rt oster d 1 1 in ormal bject and in p t ent w th b orm 1 d enoc rt c 1 f 1 on (Co rt y f Ch ty N P t 1 J Clin I est. 34 819 906 J 1955)

ology from that due to other causes In the small number of cases studied postoperatively the ACTH corticosteroid re sponse seemed a useful index of the efficacy of treatment

The authors draw two additional conclusions from their data (1) Increase of Porter Silber reactive substances meas ured as plasma 17 hydroxycorticosteroids which occurred

in advanced pregnancy in a patient with Addison s disease was due to an extra adrenal source which could not be stimulated further by ACTH (2) The increasing concentration of these substances in normal pregnancy may be due to an extra adrenal source and to the adrenal cortex but the excessive corticosteroid increase following ACTH must be due to *enhanced responsiveness of the adrenal cortex itself*

[These data confirm the clinical usefulness of the determination of plasma 17 hydroxycorticosteroids The recommended technic is less difficult than the usual methods and *is suitable for routine use in* any well equipped hospital laboratory The results reported in these papers are like those obtained by a number of other observers using more elaborate technics It should be emphasized that the basal steroid level is often much less informative than the response to ACTH —Ed.]

Effect of 9α Fluorohydrocortisone on Adrenal Hyperfunction in Cushing s Syndrome is reported by C L Cope and R J Harrison[8] (London) Both cortisone and 9α fluorohydrocortisone promptly inhibit the high urinary ketosteroid output in the adrenogenital syndrome due to adrenal hyperplasia 9α Fluorohydrocortisone has an advantage over cortisone or hydrocortisone in studies of adrenal inhibition since the end products of its metabolism are excreted in a form different from the naturally occurring adrenal hormones The authors paid particular attention to the excretion of hydrocortisone which seemed likely to provide the most sensitive and specific index of changing adrenal function

Man 25 had marked change in appearance and gain in weight typical florid Cushing s appearance purple striae moonface thin skin blood pressure of 170/130 normal serum electrolytes and glucose tolerance test and no evidence of osteoporosis Subtotal adrenalectomy revealed bilateral adrenal hyperplasia with a small probably nonfunctioning adrenal adenoma

Hydrocortisone excretion was high 400 500 µg daily (normal 40 200 µg) 9α Fluorohydrocortisone was given in daily *doses of 2 5 10 and 15 mg With doses above 2 mg* output of hydrocortisone in the urine was inhibited returning to normal levels when the drug was withdrawn Excretion of 17 ketosteroids 17 ketogenic steroids tetrahydro E and tetrahydro F were unchanged

The finding that 9α fluorohydrocortisone can inhibit adrenal activity in Cushing s syndrome due to adrenal hyperplasia raises hopes that a diagnostic procedure can be developed for this condition similar *to that used for the* adrenogenital syndrome and that Cushing s syndrome due to

(8) B M J 2 457 460 Ag 20 1955

adrenal tumor may prove insensitive fluorohydrocortisone

628 carbo adren mor ext blood ater no

* [This observation is comparable in a pati of carbohydrate active corticosteroids to the (see 1954-55 YEAR BOOK, p 620) that cortison of 17 ketosteroids in patients with excessive andr adrenal hyperplasia. They found that cortisone did not of 17 ketost roids in a patient with Cush ng s syndrome cause cortisone itself is an effective precursor of 17 ketos fluorohydrocortisone test may prove valuable in distinguisha plasia from tumor in Cushing s syndrome. "Tests of this sort may ever prove misleading in some instances since Gallagher *et al* have scribed a patient with metastatic masculinizing carcinoma of the adrenal which was suppressed by exogenous cortisone—Ed.]

Aldosterone Observations on Regulation of Sodium and Potassium Balance were made by John A. Luetscher Jr and Robert H Curtis[9] (Stanford Univ) Aldosterone is found in the adrenal cortex as well as in increased *amounts in the* urine of patients with nephrosis congestive heart failure

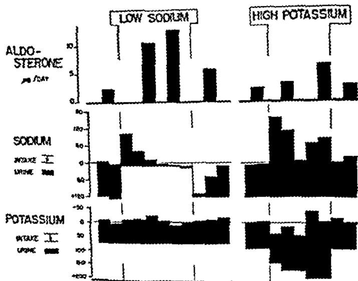


Fig 104 —Compa son f ffect f low sod m d h gh pot m eg men on ld s eron output f on bala es f sod m d pota m heal hy m 41 I tak f sod m pot m h rt 3 dow f m k d d ly ou p t d ra ed by h ght f bla k block Scale how bala *mEq /day* D r g both pe ental period the w t ongl neg t sod m bal d cated by x en m f output block ho balanc) (Courte y f L etsch J A) d C A I t M d. 43 658 6 6 Octobe 1955)

[9] M d. 43 658 666 Octobe 1955

in adrenal hyperplasia and toxemia of pregnancy and in tumors of the adrenal cortex which secrete aldosterone It is over 30 times more potent than desoxycorticosterone in reducing sodium excretion and has a comparable effect in increasing the output of potassium In excess aldosterone has some properties of the glucocorticoids e g corticosterone or hydrocortisone It has not shown anti inflammatory properties in the small doses thus far tested The hormone appears in normal amounts in urine of normally hydrated patients without obvious relation to renal function and diuresis but is not present in the urine in Addison s disease or after bilateral adrenalectomy

The output of aldosterone in normal man is closely related to sodium and potassium intake and balance which suggests an effort to return the altered balance toward normal (Fig 104) The pituitary has little control over its secretion

Metabolic Studies with Aldosterone in a Patient with Addison s Disease and in a Normal Subject were made by Solomon I Griboff Roslyn Wiener Julius Eisenberg Angelo Iannaccone and Louis J Soffer[1] (Mount Sinai Hosp New York) Aldosterone was administered intramuscularly in a dosage of 100 µg /day for nine days to the patient with Addison s disease and 200 µg a day for five days to the normal subject In this dosage aldosterone had a modest sodium and chloride retaining effect in both subjects and in the patient with Addison s disease some potassium diuresis occurred

Directly after discontinuation of therapy there was a marked retention of sodium chloride and potassium This effect lasted about 48 hours in the patient and somewhat longer in the control

In the patient some decrease in the serum concentration of potassium occurred during administration of aldosterone In both subjects there was a slight expansion in the extracellular fluid compartment not associated with any significant change in the total body water or body weight and a considerable increase in excretion of the formaldehydogenic fraction and a slight increase in excretion of the neutral 17 ketosteroids The absolute increase in urinary quantity of the formaldehydogenic fraction was considerably greater than the amount of hormone given

(1) Metabolism 4 289 294 July 1955

With the small dosages of aldosterone no change in blood pressure glucose tolerance curve or response to the water load test was observed in either subject and there was no peripheral eosinopenia in the control The patient with Addison s disease was well maintained through a moderately severe upper respiratory infection with 100 μg aldosterone a day

Spontaneous Hypopotassemia Hypomagnesemia Alkalosis and Tetany Due to Hypersecretion of Corticosterone Like Mineralocorticoid are reported by Ivan J Mader and Lloyd T Iseri[2] (Detroit Receiving Hosp)

Woman 33 hospitalized due to tetanic contractions of the hands for one day and muscle weakness pain and cramps and numbness of the extremities for two months showed hypertension hypertensive retinopathy presence of Chvostek s sign and slight cardiomegaly Tetany was relieved by rebreathing expired air but Trousseau s sign remained

Laboratory examination revealed hypopotassemic alkalosis with plasma levels of potassium 1 6 sodium 143 chloride 84 and CO_2 combining power 42 mEq /L Serum calcium and magnesium levels were 4.25 and 1 1 mEq /L Inorganic phosphorus level was 2 7 mg / 100 ml Results of renal function tests and presacral air insufflation studies were normal

Trousseau s sign was still present after calcium gluconate intravenously Potassium chloride intravenously did not affect the muscle irritability After supplementary potassium chloride therapy of 80 mEq /day plasma levels were sodium 150 potassium 3 7 chloride 101 and CO_2-combining power 28 mEq /L Muscle irritability gradually disappeared and strength improved

Metabolic studies indicated excessive excretion of potassium and magnesium in urine and stool with concomitant retention of sodium Potassium supplements resulted in uptake of potassium and loss of sodium from the cells Alkalosis was attributed to potassium depletion

Urine studies revealed increased excretion of corticosterone like steroid by chemical tests and increased salt retaining corticoid by the bioassay method

The syndrome could be explained by oversecretion of corticosterone like mineralocorticoid presumably aldosterone The clinical features of the case are identical with those of a case presented by Conn termed primary aldosteronism

Removal of an adenoma from the left adrenal gland restored blood pressure and electrolytes to normal The tumor contained 1 4 μg aldosterone/Gm

[Since Conn s descript on of this syndrome (ee 1955 56 YEAR BOOK p 612) several other ca es have come to l ght In add t on to the one described here Foye and Fei htmeir have also reported a case in which

(2) Am J Med 19 976 988 Decembe 1955

the source of mineralocorticoid was a *carcinoma* (Am J Med 19 966 1955) —Ed]

Variations in Renal Excretion of Sodium Independent of Change in Adrenocortical Hormone Dosage in Patients with Addison s Disease were studied by Jack D Rosenbaum Solomon Papper and Milton M Ashley [3] The adrenal cortex has been known to affect renal sodium excretion but the precise role of adrenocortical hormones in its physiologic regulation is not well defined Inferential evidence that normal regulation is associated with adrenal hormone activity was obtained when it was observed that the urine of normal men on salt poor diets had enhanced salt retaining activity

Three patients were studied while receiving desoxycorticosterone acetate alone and with cortisone both medications at constant dosage In two renal sodium excretion varied with change in posture but in the other no definite response was noted During and after venous congestion of the thighs the one patient tested had diminished natriuresis All three patients had increased sodium excretion after infusion of a hypotonic sodium solution In one in whom it wa studied the diurnal excretory rhythm for water and electrolyte was normal Changes in sodium excretion were related to alterations in tubular reabsorption rather than in filtered sodium load

Although cortisone appeared to maintain the integrity of the regulatory mechanisms for sodium excretion changes in excretion were presumably independent of change in hormone activity The same stimuli are known to produce changes in excretion of sodium in normal subjects to about the same degree However since in the three patients with Addison s disea e adrenocortical hormones were exogenously supplied at a constant rate the changes in sodium excretion could not be ascribed to alterations in level of adrenocortical hormone activity The observations indicate that large and appropriate changes in sodium excretion occur independently of changes in adrenocortical hormone level suggesting that one role of the adrenal cortex in the regulation of sodium excretion is of the permissive type

• [The concept of permissive action of adrenal steroids is well established in regard to carbohydrate and protein metabolism this demonstration of a similar effect in electrolyte control is of great practical importance since it indicates that electrolyte alterations of the reaction to injury need not necessarily reflect increased adrenal secretion —Ed]

(3) J Clin Endocrinol 15 1459 14 4 December 1955

Congenital Adrenal Hyperplasia with Hypertension Unusual Steroid Pattern in Blood and Urine is described by Walter R Eberlein and Alfred M Bongiovanni[4] (Univ of Pennsylvania) In congenital virilizing adrenal hyperplasia synthesis of 17 hydroxycorticosterone compound F is deficient Plasma 17 hydroxycorticosteroids are low despite increased endogenous adrenocorticotropin and do not rise when ACTH is administered Excretion of compound F metabolites is low and excessive excretion of pregnane 3α 17α 20α triol suggests a block between 17 hydroxyprogesterone and compound F

A pseudohermaphrodite aged 8½ with congenital adrenal hyperplasia and severe hypertension displayed adrenal steroid metabolism different from any recorded in this syndrome without hypertension Before treatment the plasma 17 hydroxycorticosteroids were 24 7 μg /100 ml and the conjugated steroids 52 3 μg /100 ml compared with the normal of 8 μg Paper chromatography of unhydrolyzed plasma revealed a single steroid characteristic of compound S (delta 4-pregnene 17α 21 diol 3 20 dione) and of hydrolyzed plasma tetrahydro S (pregnane 3α 17α 21 triol 20 one) No traces of compound F or its normal metabolites were found

From the ketonic fraction of urine tetrahydro S was isolated in crystalline form and was the predominant C 21 steroid Its excretion averaged 24 mg /L of urine or 18 mg / 24 hours Until now this steroid had been isolated in large amount only from the urine of patients with adrenocortical carcinoma The predominant steroid in the nonketonic fraction also isolated in crystalline form was pregnane 3α 17α 20? 21 tetrol This steroid has not been isolated previously A second steroid from the ketonic fraction was tentatively identified as tetrahydro desoxycorticosterone (pregnane 3α 21 diol 20 one) previously isolated from human urine after administration of desoxycorticosterone but never before reported as a spontaneous occurrence Pregnane 3α 17α 20α triol was also isolated from the nonketonic fractions

Trace amounts of more polar nonketonic and ketonic steroids were isolated and were probably 11 desoxy compounds No traces of compound F corticosterone or their metabolites were found Of the neutral 17 ketosteroids etiocholanolone were preponderant 11 oxygenated 17 ketosteroids absent

(4) J Clin E doc ol 15 1531 1534 December 1955

During therapy with hydrocortisone the hypertension regressed The unusual steroids in the urine disappeared and were replaced by normal metabolites of compound F

These findings suggest an isolated and complete deficiency of adrenal enzymes concerned with introduction of a hydroxyl group into the steroid molecule at C 11 A deficiency of 11 β hydroxylase may be characteristic of the disease when complicated by hypertension The resultant adrenal secretion of desoxycorticosterone may explain the hypertension

• [This important article proves the presence of a second type of metabolic defect in the adrenogenital syndrome In addition to failure of 21 hydroxylation (see 1954 55 YEAR BOOK p 612) resulting in accumulation of the potentially androgenic substance 17 hydroxyprogesterone it now appears that there may be failure of hydroxylation at the 11 carbon resulting in accumulation of potent sodium retaining steroids such as desoxycorticosterone The fact that a specific enzymatic defect can be so clearly correlated with a specific clinical syndrome further proves the importance of fundamental research in clarifying purely practical clinical problems — Ed]

Chromosomal Sex in Gonadal Dysgenesis (Ovarian Agenesis) Relationship to Male Pseudohermaphrodism and Theories of Human Sex Differentiation Melvin M Grumbach Judson J Van Wyk and Lawson Wilkins[5] (Johns Hopkins Univ) studied 22 patients of whom 20 were found to be chromosomal males Because of this and the histology of the vestigial gonads the name gonadal dysgenesis is advocated instead of ovarian agenesis

Normally the human embryo is potentially bisexual and is transformed into a fetus with normal male or female genital organs In gonadal dysgenesis the gonadal components derived from the germinal epithelium of the genital ridges do not develop Varying amounts of mesonephric vestiges can be identified indicating dysgenesis rather than true agenesis

The findings in both chromosomal males and females with typical gonadal dysgenesis agree with fetal castration experiments in animals Female differentiation of the genital ducts and external genitalia always occurs if fetal testes are absent apparently ovarian hormones are not necessary for this differentiation In human sex development testicular secretion has primarily a local action in determining development of the genital duct In true hermaphrodites with an

(5) J Cl E docrin l 15 1161 1193 Oct ber 1955

ovary on one side and a testis on the other the homolateral genital duct is compatible with the homolateral gonad

Chromosomal males with the usual type gonadal (testicular) dysgenesis represent the most extreme form of male pseudohermaphrodism—genetic males who are anatomically completely feminized Fetal testicular function is completely absent and the genital ducts and genitalia develop as female In patients in whom mesonephric rudiments with Leydig cells are better developed enlargement of the genital tubercle results from the masculinizing secretions Occasionally fetal testicular function on one side may initiate male sex differentiation but be insufficient to complete it The result may be a male pseudohermaphrodite with mullerian

CLASSIFICATION OF AMBISEXUAL DEVELOPMENT IN CHROMOSOMAL MALES
EFFECTS OF VARYING DE REES OF FETAL TE TICULAR INSUFFICIENCY

A Gonadal dysgenesis in chromosomal males
  1 Typical—simulating female
  2 With phallic enlargement
B Classic male pseudohermaphroditism
  1 Simulant female with feminizing testes and wolffian vestiges
  2 External genitalia ambiguous or resembling those of male
    a) Mullerian duct derivatives predominant
    b) Wolffian duct derivatives predominant
C Hypospad c males with bifid scrotum

vestiges and a hypospadic phallus (these were present in one patient)

The relation of chromosomal males with gonadal dysgenesis to pseudohermaphrodites with morphologically male gonads and ambisexual differentiation of the genital ducts or external genitalia or both is shown in the table To cause such variations fetal testicular function must have been deficient at some stage during the critical period of sex differentiation

The most likely basis for the syndrome is an unknown agent active before the eighth to ninth week in the male embryo and slightly later in the female which adversely affects the embryo or the germ plasm There is little evidence that gonadal dysgenesis is genetically determined Deleterious environmental influences may account for noninheritable but multiple defects

In Turner s syndrome in boys although there may be hy

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These findings suggest an isolated and complete deficiency of adrenal enzymes concerned with introduction of a hydroxyl group into the steroid molecule at C 11 A deficiency of 11 β hydroxylase may be characteristic of the disease when complicated by hypertension The resultant adrenal secretion of desoxycorticosterone may explain the hypertension

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(5) J Cl Endocrı 1 15 1161 1193 Oct be 1955

nick[7] (Princeton Univ) Some of the 9α halogenated adrenal steroids such as cortisone hydrocortisone corticosterone and certain derivatives of progesterone display potencies considerably in excess of the naturally occurring parent steroids both as to glucocorticoid and mineralocorticoid activity

The authors used long term adrenalectomized dogs for testing the mineralocorticoid and life maintaining activity of certain 9α halo adrenal steroids and also two halogenated derivatives of progesterone The compounds proved to be extremely efficacious for maintaining the animals in normal health and vigor The 9α fluorohydrocortisone was more active than the chlorohydrocortisone and both were much superior to DOC One halogenated adrenal steroid 9α fluorocorticosterone exhibited sodium retaining and life maintenance potency equal to that of aldosterone The minimal maintenance dose of the substance was 6 85 µg /dog/day and the dose at which marked symptoms of adrenal insufficiency appeared was 3 42 µg /day These figures are identical with those previously obtained with aldosterone tested on the same dogs

Doses of 1 2 mg /dog/day of 9α fluorocorticosterone caused Na retention and persistent but moderate elevation of the mean arterial pressure It was considered probable that administration of fluorocorticosterone in larger quantities would induce increases in blood pressure and perhaps definite hypertension A diabetes insipidus like syndrome accompanied by edema of the legs and scrotum was produced by overdosage with 9α fluorohydrocortisone

The human patient responds to the two halogenated compounds in a manner similar to the dog for clinical studies on patients with Addison s disease have shown that fluorohydrocortisone is much more active than chlorohydrocortisone

No satisfactory explanation has been offered to account for the surprising enhancement of physiologic activity of the 9α halogenated series of steroids

Metabolic Effects of 9α Fluorohydrocortisone and of Cortisone in Adrenal Insufficiency Oliver Garrod J D N Nabarro G L S Pawan and G Walker[8] (Middlesex Hosp London) compared the metabolic effects of 9α fluorohydrocortisone acetate (ΓHC) and cortisone acetate in two wom

(7) E doc l gy 57 2 0 30 A gu t 1955
(8) La t 2 367 370 A g 20 1955

pogonadism and maldeveloped testes there is hypoplasia of the testicular components and not dysgenesis with absent germinal elements In patients with anorchia masculinization does not occur at puberty but otherwise the patients are normal males In such patients testes must have been present in early fetal life and degenerated after sex differentiation

* [Although the observations outlined in the preceding article are somewhat outside the range of topics usually discussed in this section of the YEAR BOOK it seemed desirable to include them because of the light they shed on syndromes which may sometimes be confused with the adrenogenital syndrome or with other forms of abnormal sexual differentiation It has recently been reported that certain patients with Klinefelter s syndrome (absence of sperm with high urinary follicle stimulating hormone and gynecomastia) may have female sex chromatin patterns although they appear masculine on physical examination (Bradbury *et al* J Clin Endocrinol 16 689 1956) Chromosomal sex differentiation has proved to be a valuable tool in evaluating patients with adrenogenital syndrome Turner s syndrome and congenital malformation of the gonads The technic is simple and easy to apply especially if smears of the vaginal or buccal mucous membranes are used —Ed]

Treatment of Chronic Adrenal Insufficiency with Hydrocortisone Free Alcohol is reported by L de Gennes H Bricaire and B Mathieu de Fossey [6] who gave the hormone to 10 *patients with chronic adrenal insufficiency (Addison s disease)* and to 1 patient who had bilateral adrenalectomy for Cushing s disease to determine whether hydrocortisone alone could control adrenal insufficiency

In one patient treatment with hydrocortisone alone was followed by extreme deterioration In four others the serum sodium level dropped to the lower limit of normal

Woman 30 with Addison s disease was well controlled on 25 mg cortisone/day and 5 mg desoxycorticosterone acetate (DCA) twice weekly Weakness disappeared blood pressure became normal and weight approached obesity Later cortisone was replaced by 20 mg hydrocortisone/day and DCA was discontinued After three months *weakness and anorexia occurred again and she did not improve* even when hydrocortisone was increased to 30 mg daily To control the disease again administration of DCA twice weekly had to be resumed

Control of Addison s disease by hydrocortisone is inadequate unless some salt regulating hormone (e g DCA) is also given

Maintenance of Adrenalectomized Dogs with 9α Halo Adrenal and Other Steroids was studied by W W Swingle Carleton Baker Milton Eisler S J LeBrie and Leo Bran

(6) A n. endocrinol. 26 236 245 1955

Woman 58 had carinoma of the breast axillary metastases and multiple metastases in bone General condition was fair Following total hypophysectomy recovery was uneventful She received ACTH intramuscularly every six hours to 60 I U daily beginning two days before operation and throughout the study There was sodium and chloride retention on the 1st 5th days on days 6-10 there was loss of salt equivalent to the amount retained postoperatively (Total retention of sodium 263 mEq and total loss 267 mEq) Throughout the study the salt intake was unchanged (daily sodium intake 91 mEq) On days one and two the potassium balance was negative and the intake decreased No significant change in potassium balance was noted during the rest of the study (Fig 105)

The electrolyte balance in this patient indicates that the initial phase of postoperative salt retention and subsequent salt loss *can occur in the absence of the* pituitary gland when the adrenal glands are exposed to a constant dosage of ACTH Similar biphasic changes in salt balance were observed in the other patients The degree of change seemed related to salt intake and the amount of hormone present

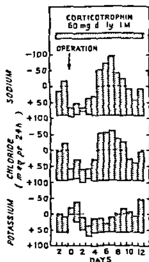


Fig 105 —M t bol h ng tot l hypophy ectomy (C urt y f M son A S La et 2 63 636 S pt 24 1955)

The data obtained from these patients indicated that the postoperative metabolic response was essentially normal despite the constant hormone dosage Furthermore the metabolic response after these operations was similar to that seen after operations on patients with intact adrenals A normal postoperative response was obtained when substitution therapy with either ACTH or cortisone was given at a constant daily dosage

From the practical standpoint when the normal pituitary gland or the adrenal glands are removed massive doses of adrenal steroids are unnecessary and the daily dose need not be varied Cortisone alone proved a satisfactory cover for adrenalectomy provided it was administered regularly for

en one with total adrenalectomy and the other with Addison s disease Both had been receiving cortisone 50 mg/day and about 6 Gm added salt for several months

The authors found in conformity with previous reports *that in adrenal insufficiency 0 5 mg FHC acetate has a much* greater sodium retaining action than 50 mg cortisone acetate and that the mineralocorticoid activity of FHC is therefore more than 100 times that of cortisone This differerce was also reflected in the salivary Na K ratios when allowance was made for the rate of salivary flow The glucocorticoid potencies of 0 5 mg FHC however, were less pro*nounced than that of 50 mg cortisone*

Cortisone unless given in unphysiologic doses or supplemented by extra sodium chloride is often inadequate for maintenance of satisfactory electrolyte balance in adrenal insufficiency The patients studied were on 50 mg cortisone a day and some extra sodium chloride during the initial control period Though urinary glucocorticoid excretion was above *normal they had a tendency to hyperkalemia* and nitrogen retention To correct this a steroid with greater mineralocorticoid action is required At present the best way of achieving this is by monthly injections of desoxycortone trimethylacetate The combination of small doses of FHC with physiologic amounts of cortisone *(20-25 mg a day)* may permit all treatment to be given by mouth Extra sodium chloride should seldom be required with thi regimen

• [Although fluorohydrocortisone gives good ele trolyte regulating control of adrenal insufficiency it is probably not entirely adequate unless supplemented by one of the potent carbohydrate regulating substances such as hydrocortisone The combination of cortisone or hydrocortisone with *fluorohydrocortisone permits balanced substitution therapy* by oral preparations —Ed]

Metabolic Response to Total Adrenalectomy and Hypophysectomy was studied by A Stuart Mason[9] (London Hosp) in eight *women with carcinoma of the breast* Metastases were present in seven Two patients had total hypophysectomy one total adrenalectomy and five total adrenalectomy and oophorectomy Cortisone was given intramuscularly twice daily to patients who had adrenalectomy and *ACTH* was given intramuscularly every six hours to patients who had hypophysectomy

(9) La et 2 632-636 Sept. 24 1955

venously during surgery may replace this in the future After surgery 500 mg cortisone was given daily and gradually tapered Many patients had stormy postoperative courses re lated to a prolonged phase of nutritional replenishment

The state of the anterior pituitary body in Cushing s dis ease is still undecided No enlargement of the anterior pitui tary body or of the sella turcica and no evidence of a baso philic adenoma were found in these patients One patient had a small nonbasophilic adenoma Crooke s hyaline baso phils and abundant hypertrophic amphophils characteristic of adrenal hyperactivity were found in all six pituitary glands studied The minute basophilic adenomas believed by Cushing to be responsible for the disease were probably in cidental findings

Role of Surgery in Therapy of Adrenocortical Hypersecre tion is decribed by Harry H LeVeen and Alton R Pruit

Woman 27 had scanty menses for seven years and amenorrhea for one year loss of libido and weight gain The face was slightly moon shaped with increase in lanugo like facial hair and coarse hairs on the chin and upper lip Breasts were normal without striae as were the external genitalia uterus adnexae and cervix Glucose and insu lin tolerance tests were normal Excretion of 17 ketosteroids was in creased to twice the upper limit of normal There was no osteoporosis by x ray

Blood pressure remained elevated for four months of observation and hirsutism and obesity became more marked Tentative diagnosis was adrenogenital syndrome and she was given 50 mg cortisone daily The 17 ketosteroid excretion remained high suggesting pres ence of an adrenal cortical tumor Increasing the cortisone to 100 mg *daily reduced the excretion only slightly No tumor was visualized on* retroperitoneal air insufflation Exploratory laparotomy disclosed both glands slightly larger than normal but no tumor The adrenals were subtotally resected and about 1 cc tissue left behind on each side The resected portion of the left adrenal weighed 17 9 and of the right 8 5 Gm Pathologic diagnosis was hyperplasia of the left adrenal

Recovery was uneventful Blood pressure became normal obesity and hirsutism disappeared 17 ketosteroid excretion was normal on three occasions regular menses resumed and she was able to conceive

The possibility of a cortical tumor in this case was sug gested when 17 ketosteroid excretion remained elevated de spite adequate cortisone dosage An apparent shortcoming in the use of this test was thus illustrated Although the only signs were hypertension and moon shaped facies the case should be considered one of adrenócortical hyperfunction A patient with a pure adrenogenital syndrome cannot exhibit

(2) J A M A 158 1438 1441 A g 20 1955

two or three days before operation Similarly ACTH in constant dosage started preoperatively provided a satisfactory cover for total hypophysectomy There is no need for an increased salt intake over the immediate period of operation A constant intake is preferable in amounts similar to those in a normal diet i e 6 8 Gm sodium chloride daily

Cushing s Disease Surgical Experience in Care of 46 Cases is reported by Oliver Cope and John W Raker[1] (Harvard Med School) Predominant physical changes were a peculiar obesity florid atrophy of the skin, hirsutism acne muscular wasting vascular fragility hypertension osteoporosis and gonadal suppression Obesity was limited to head neck and trunk with wasting of extremities The face was florid puffed and rounded supraclavicular fat pads and buffalo hump were prominent Muscular wasting the most constant sign led to fatigue the most consistent symptom Osteoporosis a cardinal sign was not always present but when severe was often associated with vertebral collapse The negative nitrogen balance led to kidney stones in 11 patients Laboratory findings included a tendency to glycosuria and elevated blood sugar levels

Simple plain x rays after proper preparation of the bowel were as reliable in diagnosis as periadrenal air insufflation Intravenous pyelograms were of no help

Surgery of the adrenal gland was the only consistently successful therapy Suppression of the anterior pituitary gland by irradiation or hormones was only sporadically successful When the disease is caused by tumor of the adrenal gland treatment is complete removal of the tumor leaving the contralateral uninvolved gland Neoplasm was found in 17 patients 5 with malignant tumors died of metastatic disease Of the 12 with benign tumors 1 died before operation and 11 were cured by resection

Bilateral hyperplasia was found in 27 patients Two patients died before operation 2 died after surgical treatment and 19 were alive and well after subtotal resection Of four who had limited resection two died from active disease and two had residual disease For consistent therapeutic effect at least 90% of adrenocortical tissue must be removed

Cortisone 100 mg was given intramuscularly 12 hours before operation and before anesthesia Compound F intra

(1) New England J Med 53 119 127 July 28 165 172 Aug 4 1955

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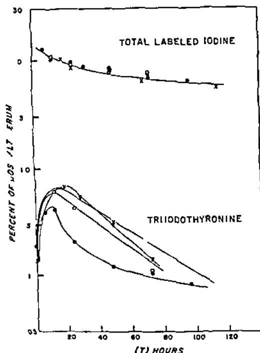
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Conversion of Thyroxin to 3 5 3 Triiodothyronine in Vivo was investigated by Rosalind Pitt Rivers John B Stanbury and Betty Rapp[4] (Harvard Med School) The principal iodinated compound of the blood is thyroxin In



F g 106—D sappea f label d od d ppea f t odothy on th blood t f p ent ft dm t t on f I l bel d thy x (Cou t y f P tt R R t l J Cl E doc l 15 616 6 0 M y 1955)

addition small amounts of triiodothyronine have been found in the blood of clinically euthyroid subjects and patients with hyperthyroidism It has not been demonstrated whether the triiodothyronine present in the peripheral blood is secreted directly by the thyroid gland or whether it is de

(4) J Cl E doc ol 15 616 6 0 M y 1955

any clinical features of adrenocortical hyperfunction but one with adrenocortical hyperfunction might have mixed symptoms

Adrenocortical hyperfunction should be treated by adrenal resection as should the adrenogenital syndrome when it does not respond to cortisone

• [This patient had adrenal hyperplasia but failed to respond to cortisone Perhaps the difficulty here was that she did not have primarily a masculinizing hyperplasia but had Cushing s syndrome Such a patient would not be expected to respond to cortisone The authors did not study 17 hydroxycorticost roids or oth r corticoids and therefore offer no information on the subject The fact that no clearcut clinical signs of Cushing s syndrome were observed does eliminate the possibility that the chief difficulty may have been overproduction of corticosteroids rather than androgens Discussion about the ideal treatment of Cushing s syndrome continues In addition to these papers recommending subtotal adrenalectomy Skanse *et al* have also reported on five patients successfully treated by subtotal adrenalectomy (Acta med scandinav 144 119 1956) —Ed.]

Therapeutic Value of ACTH and Cortisone in Experimental Burns was studied by W H A Schottler[3] (São Paulo) in mice scalded in hot water and then treated with ACTH cortisone or a mixture of both in doses of 0 5 25 mg/kg Most of the body surface was exposed to intense heat for short periods to simulate as closely as possible life endangering burns in man No beneficial effect of hormone therapy was observed Under the conditions cortisone significantly increased mortality

The clinical use of ACTH and cortisone in burn shock has been justified by the stress hypothesis Permeability of capillaries is increased in burns and adrenocortical deficiency but the mechanism is not the same Leakage of plasma in the acute stage of burn shock is not due to hormonal insufficiency Different types of stre s demand different hormone responses Previous reports have shown that cortisone protected mice from cold stress but lowered normal resistance against heat stress

The reasoning which has led to the clinical use of adrenocortical hormones in treatment of burn shock is unsound Subjective improvement noted may have been simulated by the euphoric state induced by ACTH

• [The absence of benefit from steroid treatment of animals with burns suggests that previous clinical impressions of improvement from such treatment in pa ients may have been overoptimistic. The use of steroids as nonspecific tonics" should be avoided even in the presence of severe stress unless some clear indication for their administration is present —Ed.]

(3) Endocrinology 57 445-449 Oct be 1955

tration to about 0 05 unit in 2 ml Iodine given to intact animals brings the level to negligible amounts given to thyroidectomized or thiourea treated rats it reduces the previously raised blood concentrations considerably but not to normal

In the hypophyses of the rats the affinity for Gomori s aldehyde fuchsin by the thyrotroph cells was inversely proportional to the blood concentration of thyrotropin In thyroidectomized or thiourea treated rats granulation was almost completely lost and most of the thyrotrophs appeared hypertrophied The Golgi apparatus often stained diffusely and occasionally a positive image could be seen in normal cells Some intensely stained granules were al o observed more marked in thiourea treated rats Iodine raised the affinity for aldehyde fuchsin

The results definitely show that iodine in the doses administered inhibited production of thyrotropin by the hypophysis This effect was manifest even when production of thyrotropin had previously been increased by thyroidectomy or thiourea The mechanism is not inactivation of thyrotropin already secreted into the blood stream because if this were so the original thyrotropic activity would have been restored by treating the iodinated compound with acetone and acetone was used in the experiments to isolate thyrotropin It is evident therefore that the inhibiting action exerted by iodine on the thyroid is mainly due to pituitary inhibition

Effect of Iodide on Release of Thyroid Hormone in Hyperthyroidism in 11 patients is reported by Richard E Goldsmith and Mary Louise Eisele[6] (Univ of Cincinnati) All had typical clinical signs and symptoms of hyperthyroidism and elevated BMR and thyroid I^{131} uptake Beginning 72 hours after a tracer dose of 250 μc radioiodine 40 mg 1 methyl 2 mercaptoimidazole (MMIA methimazole) was given orally every 8 hours for 16 20 days During the last 8-10 days sodium iodide 50 mg every 12 hours was added

The patients with hyperthyroidism and diffu e goiter (Graves di ease) had less iodide hormone release during NaI therapy (Fig 107) Two patients with multinodular goiter and hyperthyroidism also responded in this manner but two others had no significant change in hormone release The

(6) J Cl E doc 1 35 130 137 J ry 1956

rived from degradation of previously secreted thyroxin In an attempt to determine the source of triiodothyronine the authors chose six patients with myxedema five of whom received thyroxin until the clinically euthyroid state was nearly or entirely reached At this juncture each patient received intravenously about 500 μc I^{131} labeled thyroxin

The serum concentrations of labeled iodine and of triiodothyronine are shown in Figure 106 The upper curve is the total serum concentration of labeled iodine The extrapolated concentration at zero time was 13 9% of the administered dose/L serum The lower curves are calculated from the ratio of labeled iodine in the triiodothyronine band to that in the thyroxin band The zero points on the triiodothyronine curves are the contaminating amounts of substance in the injected solution that had the chromatographic properties of triiodothyronine

The increase in labeled triiodothyronine in the serum of the patient who received no stable thyroxin was the same as that in the other patients this suggests that the administered labeled thyroxin did not exchange with triiodothyronine previously formed in vivo from administered thyroxin The amounts of triiodothyronine found in the serum of athyreotic patients are small considerably greater amounts possibly could have been found in other tissues or in organs

The thyroid gland apparently is not essential for the formation of triiodothyronine and some other organ is able to perform the partial deiodination of thyroxin

Effect of Thyroidectomy Thiourea and Iodine on Circulating Thyrotropin and Pituitary Thyrotroph Cells in Rats is reported by Estanislao Del Conte and Maria Stux[5] (Buenos Aires) in a study of 37 animals Histologically the thyroids of rats receiving iodine thiourea or a combination of both showed the characteristic changes—increased follicular colloid and flattened epithelium marked epithelial hypertrophy and resorption of the colloid and return to normal histology

Blood concentration of thyrotropin was determined from the thyroid cytologic coefficients of guinea pigs into which blood from the variously treated and normal rats was injected Normal rats have about 0 0001 unit of thyrotropin in 2 ml blood Thyroidectomy and thiourea raise the concen

(5) Acta endocrin 1, 20 46-56 November 1955

still breast feeding an infant aged 4 months Uptake of I^{131} by the thyroid gland was 33% at 4 hours 52% at 24 hours and 61% at 48 hours Concentration of I^{131} in the breast milk was considerably greater than in the plasma at the same time The activity per liter of milk was much greater than the activity of the plasma at any time Selective concentration of I^{131} in breast milk relative to plasma concentration was of the same degree as found in saliva and gastric juice

Risk to an infant breast feeding from a mother with radioactive iodine is considerable If the isotope has been given breast feeding should immediately be discontinued As little as 25 μc radioactive iodine given to the mother may have an adverse effect on the thyroid gland of the infant

Uptake and Blood Level of Radioactive Iodine in Hyperthyroidism Robert A Newburger Solomon Silver Stephen B Yohalem and Sergei Feitelberg[8] (Columbia Univ) selected 500 consecutive patients referred for thyroid study who had had no previous thyroid therapy

Before I^{131} studies the patients were classified as normal or hyperthyroid by history physical examination BMR and tests for blood cholesterol and protein bound iodine (PBI) 404 were euthyroid and 96 hyperthyroid Each patient was given a tracer dose of I^{131} and the thyroid gland uptake measured at 24 hours The plasma PBI^{131} was determined at 72 hours Frequency distributions were constructed and the points of intersection of the curves for euthyroid and hyperthyroid patients selected as critical values

The uptake studies were not as accurately diagnostic as the levels of PBI^{131} If a critical value for PBI^{131} is taken as 0 27% of the administered dose per liter of plasma there were eight diagno tic errors or 1 6% With 61% as a critical uptake value the diagnostic errors were 36 or 7 2%

To reduce the diagnostic error of the uptake method to that of the PBI^{131} method a critical range rather than a critical value was necessary If uptakes below 42% were diagnostic of euthyroidism and above 69% diagnostic of hyperthyroidism the total error was the same as that for the PBI^{131} 1 6% Use of this diagnostic range left 127 patients or 25% of the total unclassified whereas the PBI^{131} determination attained the same accuracy with no ca es unclassified

(8) N w E gl 1 J Med 53 1 130 J ly 28 19 5

effects on hormone release were probably not due to alterations in the block produced by the MMIA

When iodide and thyroid stimulating hormone were given simultaneously to two patients receiving MMIA the rate of hormone release was the same as when MMIA was given alone The thyroid stimulating hormone probably is more important in the pathogenesis of Graves disease than in multinodular goiter with hyperthyroidism and two diseases are suggested hyper anterior pituitarism with rapid

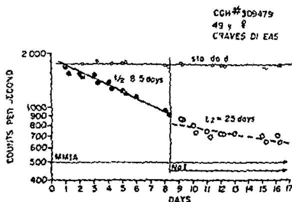


Fig 10 —H rm n relea e cu e d ing treatment with MMIA and MMIA+ N I Clos d rcl s = b rvat s d ng c ntrol pe od Open c l s = bservat ns d r ng t tment (C urte y of Go d m th R E d E) le M L J Cl E docr o 35 1 0 137 Janu y 1956)

thyroid changes and the rapid development of symptoms described by Graves and hyperthyroidism with the gradual appearance of symptoms

Iodide slows the release of formed hormone from the toxic human thyroid probably as a result of some interference with TSH at the thyroid gland

• [The preceding two articles add additional information on the mode of action of iodide on the thyroid gland but they come to contradictory conclusions as to the locus of action (see also article by Werner and others p 648) In any case the fact that iodide blocks the secretion of pre formed hormone explains the rapidity of its action in Graves disease as compared with the thiourea derivatives which block synthesis of the hormone but do not prevent secretion of pre formed thyroxin —Ed.]

Excretion of Radioactive Iodine in Human Milk H Miller and R S Weetch[7] (Sheffield) report on a woman aged 23, given a tracer dose of 29 5 μc radioactive iodine while

(7) Lancet 2 1013 Nov 12 1955

preparation containing 0 5 mg iodine (potassium iodide) per capsule This preparation was chosen because of its relatively high iodine content The I^{131} uptake by these subjects was measured before the test period after 5 9 days on the drug and in four 14 or more days after it was stopped

The uptake was lowered slightly in two subjects and increased slightly in one Three seemed to have uptake blocked as judged by drops of 24 11 and 16% and significant rebound after the drug was stopped One had a sharp fall in uptake associated with marked increase in well being Study for possible hyperthyroidism was continued Another seemed to have been blocked at the onset of the test then recovered the cause of the block is unknown

This scattered response was not unexpected considering that such variables as the iodine from food differences in absorption from the bowel and considerable range of avidity of the normal thyroid for iodine will cause individuals to react differently The important fact is that some subjects were apparently blocked during the period of drug intake and recovered after stopping it The effect noted is probably due to the iodine content of the vitamin mineral mixture

Adenomatous Goiters and Serum Precipitable Iodine William V Baker William W Engstrom and Blanch Markardt[2] (Marquette Univ) describe their experiences with the use of the serum precipitable iodine (SPI) level as a laboratory aid in appraising whether a patient with an adenomatous goiter is euthyroid or hyperthyroid No cases of Graves disease (exophthalmic goiter) were included The study group consisted of 81 women and 9 men aged 33 82 with a mean of 64 1 years Most of them were hospitalized for conditions other than thyroid disease

In this series 59 patients (65%) were ultimately categorized as euthyroid in these the SPI level varied from 2 5 to 6 9 µg /100 ml of blood (mean 5 µg) Of the patients without thyroid disease 91% had a range of from 3 5 to 7 µg (mean 5 1)

Of the 23 patients proved to be hyperthyroid in only 10 were the signs and symptoms of hyperthyroidism sufficiently definite to allow a diagnosis of hyperthyroidism before administration of antithyroid drugs or before subtotal thyroidectomy In 15 patients the SPI elevation was *minimal*

(2) A M A Arch Int Med 96 44 50 July 1955

Pitfalls in Diagnostic Use of Radioactive Iodine Solomon Silver Stephen B Yohalem and Robert A Newburger[9] (Mount Sinai Hosp New York) report on 113 patients in whom normal BMR and serum protein bound iodine (I^{127}) confirmed the clinical impression of a euthyroid state Hyperthyroid values for I^{131} uptake (over 55% at 24 hours) or protein bound I^{131} (over 0 3% of administered radioactivity per liter of serum at 72 hours) were present in all

An elevated I^{131} uptake with normal PBI^{131} was found in 33 patients with and without goiter only 2 of whom had previously been hyperthyroid Normal radioiodine uptake and a high PBI^{131} were found in 51 patients and both I^{131} uptake and PBI^{131} were elevated in 29 More than 90% of the latter two groups had been successfully treated for hyperthyroidism by surgery or radiation The mechanisms involved may possibly be related to a reduced total bodily pool of miscible iodide in the first group and to a low thyroidal pool of hormonal iodide in the second and third groups In addition a decreased renal clearance of iodide might produce similar discordant results

In determining the status of a patient with thyrotoxicosis who has received therapeutic doses of I^{131} the best guide is the clinical state of the patient The BMR and the PBI (stable) are the two best laboratory aids The I^{131} studies are the least valuable and can be most misleading Awareness of these false hyperthyroid results with I^{131} testing will prevent unnecessary treatment of normal subjects and further treatment of persons cured of hyperthyroidism with resulting myxedema

• [Once again it must be emphasized that radioactive iodine studies are misleading in treated hyperthyroidism and that radioactive iodine should *not* be used for following the course of therapy (see 1954 55 YEAR BOOK p 591 1955 56 p 587 589) —Ed]

Interference with Uptake of Radioiodine Tracer during Administration of Vitamin Mineral Mixtures was studied by Lawrence A Kohn and Edna B Nichols[1] (Univ of Rochester) to try to explain the occasional low value of radioiodine uptake found in tracer studies

Eight apparently euthyroid persons none of whom had been taking vitamin mineral supplements were given daily two capsules of gevral® a popular polyvitamin mineral

(9) J A M A 159 15 Sept 3 1955
(1) New England J Med 253 86-287 Aug 18 1955

preparation containing 0 5 mg iodine (potassium iodide) per capsule This preparation was chosen because of its relatively high iodine content The I^{131} uptake by these subjects was measured before the test period after 5 9 days on the drug and in four 14 or more days after it was stopped

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(2) A M A A h I t M d 96 44 50 J ly 1955

7 9 µg /100 ml In many of the thyrotoxic patients hyper thyroidism had been present for a long time without the patient being aware of his difficulties It may be that many of these patients become temporarily acclimatized ' to some extent to their chronically altered state of metabolism or the normal controlling mechanisms of thyroid function may still be largely intact

Present studies indicate that it would be a rare occurrence to find a hyperthyroid patient with an initial SPI below 7 µg /100 ml or especially below 6 5 µg Further a level above 7 µg *usually indicates hyperthyroidism Since most* thyrotoxic patients with adenomatous goiters exhibit min imal elevations of SPI it is important not to ignore even slightly elevated values

Since the SPI contrary to the BMR is not influenced by as many extrathyroidal factors and since it is easier to per form in the elderly it is felt to be of greater value in appraisal of total functional state of the adenomatous goiter

Further Evidence That Hyperthyroidism (Graves Dis ease) Is Not Hyperpituitarism Effects of Triiodothyronine and Sodium Iodide on the 24 hour thyroid I^{131} uptake in Graves disease were studied by Sidney C Werner Maryloo Spooner and Howard Hamilton[3] (Columbia Univ) The *same clinical chemical and radioiodine methods used in* earlier studies were used

Nineteen patients with definite active Graves disease who received 0 07-0 75 mg triiodothyronine daily for eight days showed an average 24 hour I^{131} uptake before treat ment of 56% and at the end of treatment of 62% No uptake less than 36% was noted after therapy In six patients a dose of 2 mg triiodothyronine daily was given for six days and in another patient 1 mg daily for the same length of time *The intensity of flare up of symptoms required cessation of* therapy at this point No significant suppression of thyroid I^{131} uptake occurred uptake averaged 71% before and 63% at the end of treatment

Ten patients had a recent history of onset of eye signs of Graves disease but had no evidence of hyperthyroidism Although a small but probably significant depression of I^{131} uptake occurred in two patients given daily doses of 1 mg triiodothyronine daily doses of 75 150 and 500 µg for

(3) J Clin Endocr 1 15 715 723 J n 1955

eight days caused no significant change With the 75 µg dose average I^{131} uptake before treatment was 37% and at the end 36%

In six patients Graves disease was brought to remission by definitive therapy and remission was sustained for one or more years They were then given triiodothyronine The 24 hour thyroid uptake of I^{131} averaged 26% before and 9% after therapy In all but one instance uptake fell to less than 20% following the use of the drug

In patients with no evidence of thyroid dysfunction given 70 or 75 µg triiodothyronine for eight days the 24 hour I^{131} uptake before therapy averaged 35% and at the end 11% In only one instance did uptake fail to decrease to less than 20% In this patient an uptake of 1% was obtained when the dose was increased to 150 µg daily for eight days

Thyrotropin (10 units intramuscularly daily for three days) caused no significant change in the average thyroid I^{131} uptake or average serum precipitable iodine (SPI) level in 22 patients with active hyperthyroidism In eight euthyroid patients with early signs of Graves disease the I^{131} uptake showed little increase but the level of SPI was significantly elevated

A marked decrease of uptake of I^{131} and SPI level resulted when sodium iodide (0 7 11 2 mg daily) was given to patients with active Graves disease The I^{131} uptake was increased only to a limited extent when thyrotropin was injected whereas concentration of SPI lowered almost to normal by iodide therapy increased sharply and attained levels higher than the original ones

The evidence suggests that (1) Graves disease is not caused by hyperpituitarism (2) iodides act directly on the thyroid cell and not by interference with the action of thyrotropin and (3) the difference in response to triiodothyronine between patients with active Graves disease and those with other related conditions provides a useful diagnostic test

Response of I^{131} Treated Thyroid Gland to Thyrotropic Hormone was studied by Jorge M Martin and John B Stanbury[4] (Boston) who observed the effect of thyrotropic hormone on the thyroidal uptake of I^{131} and the serum concentration of protein bound iodine (PBI) in 12 patients pre

[4] J Cl E docri 1 15 811 817 J ly 1955

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(4) J Cl E doc 1 15 811 817 July 1955

viously treated with I^{131} for hyperthyroidism and in 6 subjects in the euthyroid state

The response to administration of thyrotropic hormone appeared to vary with the functional state of the thyroid gland While the thyroid glands of some of the I^{131} treated patients responded to administration of thyrotropin others failed to do so Three patients treated before had normal control values for serum PBI and thyroidal I^{131} uptake These three also failed to show a significant response to thyrotropic hormone Three others of the same group responded One of them had an unusually vigorous response within 24 hours after a single injection of 10 USP units the thyroid gland was enormously enlarged The gland was tender and warm to touch and there were clinical signs of thyroid overactivity including transient auricular fibrillation Serum concentration of PBI and thyroidal uptake of I^{131} increased Needle biopsy specimens taken at the height of the reaction and while it was subsiding two days later showed no evidence of an inflammatory reaction or interstitial hemorrhage Five days later the serum concentration of PBI was normal

It has been shown both in the human thyroid and in that of the rat that after I^{131} radiation there may be persistent cellular hypertrophy In the rat the hypertrophy seems to depend on thyrotropic hormone stimulation attendant on reduced functional capacity of the remaining thyroid gland It may well be that in patients who did not respond to thyrotropic hormone remnants of thyroid tissue were functioning at maximal capacity and were unable to respond to further thyrotropin over and above that derived from their own pituitary glands The possibility cannot be excluded however that I^{131} impaired directly or indirectly the capacity of the thyroid cell to respond to thyrotropin Neither can the possibility be excluded that had thyrotropin been administered in higher dosage or over a prolonged period there might have been significant stimulation of the thyroids of those I^{131} treated patients who failed to respond to the dosage given

Auricular Fibrillation Following Prolonged Use of Thyroid Extract is most uncommon It was observed in a patient by Emanuel Hellman[5] (New York)

Woman 53 had taken 3 gr thyroid daily without interruption for

(5) J A M A 159 526 Sept 3 1955

six years for mild obesity At onset BMR had been —10% For 20 years she had had intermittent mild swelling of the ankles toward the end of each day During the four weeks precedin hospitaliza tion she received mercurial diuretics with good results

Physical examination revealed a normal sized thyroid and no ex ophthalmos Eyegrounds were normal There was fine tremor of the hands The heart was not clinically enlarged There was a grade 2 systolic murmur at the apex not transmitted or influenced by change of position or exercise Cardiac rhythm was grossly irregular with about 100 beats/minute The lungs were clear abdomen normal and there were no neurologic findings The legs showed some pitting edema The ECG revealed auricular fibrillation

Thyroid medication was stopped and she was put on low salt diet and phenobarbital Edema auricular fibrillation and apical systolic murmur soon disappeared and did not recur

Development of hypermetabolism simulating preci ely the picture of full blown thyrotoxicosis has been reported in pa tients receiving large amounts of thyroid Usually endog enous hyperthyroidism masked as heart disease is associated with auricular fibrillation In general auricular fibrillation occurs in 6-34% of hyperthyroid patients However only three cases of auricular fibrillation and one case of auricular flutter arising after thyroid administration to a euthyroid subject have been previously reported

• [Three grams of desiccated thyroid is ordinarily considered a safe dose to give to a euthyroid person Hellman s patient shows that even this phys ologic dose may be dangerous One wonders moreover whether obesity is a good indication for administration of thyroid in a euthyroid pat ent —Ed]

Thyroid Function Following Hypophysectomy in Man was studied by M C Li J E Rall J P MacLean M B Lipsett B S Ray and O H Pearson[6] (New York) in 35 pa tients with metastatic cancer Completeness of hypophysec tomy was evaluated on the basis of absence of urinary go nadotropins and occurrence of adrenal crisis on cortisone withdrawal

Complete hypophysectomy produced both laboratory and clinical evidence of profound myxedema Radioiodine uptake by the thyroid was lower than values reported in patients with spontaneous panhypopituitarism or pituitary myxede ma Within four weeks of total hypophysectomy the serum protein bound iodine (PBI) and uptake of I^{131} were in the range of myxedema and clinical hypothyroidism developed in four to eight weeks In the seven patients with incomplete

(6) J Cl E doc 1 15 12 8 1238 Octobe 1955

hypophysectomy the serum PBI and uptake of I^{131} were unaffected or fell only transiently

Serum cholesterol level did not rise uniformly in all patients with complete hypophysectomy The reason for this was not clear It was apparently not related to food intake or state of debility Serum cholesterol level has also been reported by others to be unaffected by pituitary myxedema

Hypothyroidism following complete hypophysectomy does not differ from that of primary myxedema Enlargement of the heart was not seen presumably because considerable time is required for development of pericardial effusion and dilatation

Laboratory and clinical evidence of hypothyroidism is a good index of complete hypophysectomy

Struma Lymphomatosa Primary Thyroid Failure with Compensatory Thyroid Enlargement According to Penn G Skillern George Crile Jr E Perry McCullagh John B Hazard Lena A Lewis and Helen Brown[7] (Cleveland) struma lymphomatosa is not chronic thyroiditis In 36 patients (33 women) aged 12 59 in whom the diagnosis was proved by needle biopsy 10 were symptomatically hypothyroid and 2 myxedematous All had diffusely enlarged goiters with smooth surfaces and usually of firm consistency None were nodular The goiters had usually been present less than two years

Laboratory studies revealed predominantly low BMR s elevated serum cholesterol low normal serum total protein bound iodine (PBI) low or low normal serum butanol extractable PBI and abnormal lack of response to thyroid stimulating hormone (TSH) The serum gamma globulin was usually increased and the albumin was decreased in 16 of 20 patients probably due to thyroxin deficiency This change could be measured by the serum colloidal gold test to which the reactions were positive in 20 of 25 patients I^{131} uptake by the thyroid varied from low to high

Total PBI alone is of little aid in the diagnosis of thyroid failure in most patients with struma lymphomatosa Butanol extractable PBI although more accurate is also not definitive Serum cholesterol *serum lipoprotein and* I^{131} uptake are not accurate indicators of thyroxin deficiency or mild thyroid failure The TSH test is a simple and accurate

(7) J Cl Endocrin 1 16 35 54 Ja n ry 1956



P et eatment Post t eatm t

F g 108 —Goit g fica tly decr sed b 3 g f d ceated thy d da'ly (Cou y f Skillern, P G et / J Clin Endocri l 16 35 54 J ry 1956)

method of differentiating struma lymphomatosa from non toxic adenomatous goiter in the absence of hyperthyroid ism The serum colloidal gold test is a simple inexpensive qualitative and sensitive diagnostic aid in most patients with struma lymphomatosa when correlated with other clinical and laboratory findings

Needle biopsy specimens in all 36 patients showed hyper plasia of the thyroid cells usually with oxyphilia in the cyto plasm lymphocytic infiltration and fibrosis The similar

pathologic findings in the thyroid glands of patients with primary thyroid failure without goiter indicate that the two conditions are probably clinical variants of the same disease

Since struma lymphomatosa is primary thyroid failure with compensatory goiter the treatment of choice is sufficient desiccated thyroid to depress the excess production of endogenous TSH In most patients thyroid significantly decreased the goiter size within two months but usually not to normal (Fig 108) The usual dosage was 3 gr daily Patients with struma lymphomatosa are more sensitive to desiccated thyroid than euthyroid patients and the dose may have to be reduced Desiccated thyroid should be given permanently Iodine should not be used

The incidence of clinical hypothyroidism after thyroidectomy is high Residual tissue may undergo further hyperplasia under TSH stimulation and the goiter reappear Since struma lymphomatosa is a failing gland with compensatory enlargement surgery is not indicated

Tolerance of Patients with Myxedema for Thyroid Richard Goldsmith and John B Stanbury[8] studied five patients with primary myxedema of 6 240 months duration four with post thyroidectomy myxedema and three without myxedema Desiccated thyroid was started at 30 mg daily and increased at about fortnightly intervals until earliest evidences of drug induced thyrotoxicosis appeared Patients were observed for clinical response basal metabolic rate body weight and protein bound iodine (PBI) concentration in the serum

Average daily dose of about 0 6 Gm desiccated thyroid was required to produce symptoms of thyrotoxicosis in the myxedema groups and an average of about 0 4 Gm in the other three patients The BMR and serum PBI concentrations were similar in the two groups at the first signs of thyrotoxicosis when thyrotoxicosis became marked BMR averaged 10% in the myxedema groups and 12% in the others Average serum PBI concentrations were 9 6 and 11 2 μg/100 ml respectively Patients with myxedema lost an average of 9 5% of body weight whereas those without myxedema averaged a 4% loss

Once normal needs are met tolerance to additional desiccated thyroid of patients with myxedema is similar to that

(8) J Clin E doc 1 15 568 5 5 May 1955

of euthyroid subjects During early weeks of therapy responses of BMR and serum PBI concentration were slightly greater in myxedematous patients but these differences were quickly dissipated at higher dosages Presumably small doses in the euthyroid patient only inhibit the anterior pituitary and substitute for intrinsic thyroid hormone production

Certain patients with myxedema—the very young and the elderly the arteriosclerotic and those with angina pectoris or congestive heart failure—may be peculiarly responsive to desiccated thyroid at onset of therapy These patients will often adjust to doses not previously tolerated if smaller doses are used initially Results of therapy in these patients may have fostered the concept that the patient with myxedema is less tolerant of desiccated thyroid but after the euthyroid state has been restored he tolerates it as well as the euthyroid patient

Hyponatremia in Primary Myxedema is reported by Robert H Curtis[9] (Mount Zion Hosp San Francisco)

Woman 66 had puffiness of the eyes hair loss and weakness for 10 years high serum cholesterol level and low BMR On thyroid medication she lost weight and cholesterol returned to normal but without advice she stopped medication When seen again seven years later she was obese and sluggish in movement and speech with a low voice and thickened enunciation Scalp hair was thin and axillary pubic eyebrow and yelash hair absent Soft but nonpitting edema was generalized particularly marked periorbitally She had a malar flush hypertrophic gums that bled easily minimal tongue enlargement basilar pulmonary rales and cardiomegaly Laboratory work revealed anemia albuminuria elevated cholesterol level BMR —30% protein bound iodine 2 µg /100 cc I uptake 7% before and after thyrotropic hormone Serum sodium level on three occasions was 105 110 and 110 mEq /L serum chloride 71 4 70 6 and 62 6 mEq /L CO 22 7 and 18 7 and potassium 3 5 and 4 mEq /L Excretion of sodium and chloride was low

The clinical course remained unchanged for the first nine days of hospitalization She then became less responsive and her appetite decreased An attempt was made to balance abnormal electrolytes with isotonic saline She was given 0 1 gr USP thyroid and 0 25 gr the following day but she continued to deteriorate and died two days after thyroid therapy was begun Autopsy revealed marked generalized edema The thyroid gland was replaced by fibrous tissue

• [Perhaps th low serum electrolytes in this patient can be explained by the high serum lipid content The authors studied only the serum cholesterol which was high and they do not mention whether the plasma was milky The mechanism of the spuriously depressed electrolyte levels in

(9) Int. Med 44 376 384 F bru ry 1956.

lactescent serum is discussed by Albrink (p 711) In any case if hyponatremia was truly present in an edematous patient the proper treatment would have been hypertonic rather than isotonic saline and if adrenal supportive treatment was needed steroids (e g intra venous hydrocortisone) rather than ACTH should have been given for rapid response in this desperately ill patient —Ed]

Effect of l Triiodothyronine Alone and Combined with l Thyroxin in Nonmyxedematous Hypometabolism Preliminary Report *is made by* A Stone Freedberg George S Kurland and Milton W Hamolsky[1] (Harvard Med School) Many patients have persistently low BMR s and such symptoms associated with thyroid deficiency as muscle or joint aching or stiffness chronic fatigue lethargy facial or periorbital puffiness but large doses of thyroid or l thyroxin do not elevate the BMR or relieve the symptoms Such patients may be unable to absorb convert to an active form or metabolize l thyroxin The two patients reported were previously unresponsive to dessicated thyroid or l thyroxin but were benefited by triiodothyronine alone or combined with l thyroxin

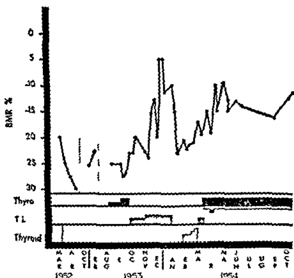
Man 29 had been tired and logy for four years Increasing doses of desiccated thyroid caused insomnia palpitation warmth and perspiration but the BMR and uptake of radioactive iodine remained low Without medication BMR varied from —26 to —30% and the 24 hour uptake of I by the thyroid gland was 33% Serum cholesterol values ranged from 227 to 253 mg /100 ml and serum protein bound iodine was 5 µg /100 ml

Figure 109 shows the experimental data l Thyroxin did not alter the clinical state l Triiodothyronine had only a slight effect in dosage of 70 µg daily but with 105 µg BMR progressively increased and the serum cholesterol level fell slightly He became alert and active and stated he felt normal When a placebo was substituted BMR fell promptly and the serum cholesterol level increased Severe lethargy fatigue and puffiness of the eyes returned Desiccated thyroid up to 4 gr daily for 1 month had little effect 70 µg l triiodothyronine for 14 days had no further effect but when 0 2 mg l thyroxin was administered with 35 µg l triiodothyronine the BMR began to rise An additional 35 µg l triiodothyronine further increased the rate but induced insomnia nervousness weakness sweating and increased appetite When the dosage was reduced to 0 2 mg l thyroxin and 35 µg l triiodothyronine BMR remained elevated but symptoms of thyroid toxicity subsided and he felt well On this dosage he remained well and the BMR remained between —12 and —3% for 7 months

Similar results were obtained in the other patient

(1) New E gl d J Med. 53 57-60 July 14 19 5

Various explanations have been considered for the results Absorption of l thyroxin or desiccated thyroid from the intestinal tract may be defective and l triiodothyronine may be more readily absorbed The deiodination of thyroxin (tetraiodothyronine) to triiodothyronine may be defective Another possibility is impaired permeability of the tissues to thyroxin but not to triiodothyronine Triiodothyronine may have been deficient and may be required for optimal metab



F g 109 —BMR d g per od f adm t t on f thy x tr od th d d ccat d thy d (Cou t y f F eedb g A S t / N w E gl d J Med 251 57 60 J ly 14 1955)

olism of thyroxin The benefit of combined triiodothyronine and thyroxin or of thyroxin immediately after a dose of triiodothyronine when each alone was ineffective is consistent with this last hypothesis

* [Hypometabolism in the presence of apparently normal thyroid function (as measured by plasma protein bound or butanol extractable iodine and radio odine stud es) has puzzled clinic ans for year Pat ents usually obtain little rel ef from des ccated thyro d The possibility that their chief trouble might be a failure of deiodination of thyroxin to triiodothyronine (as suggested in this article) needs more documentation If this mechanism proves to be valid the use of t iodothyronine will have wide pract cal appl cat on —Ed]

Association of Irradiation with Cancer of Thyroid in Children and Adolescents was investigated by Dwight E Clark[2] (Univ of Chicago) Of 14 girls and 1 boy aged 15 or younger *with carcinoma of the thyroid all had had x ray therapy* in infancy and early childhood for benign diseases of the head neck and thorax The interval between time of irradiation and diagnosis of carcinoma averaged 6 9 years The total air dose received ranged from 200 to 725 r None of the patients had had any previous thyroid disorder All but one are living and clinically free from carcinoma

From 1900 to 1950 cancer of the thyroid in persons under age 15 was diagnosed with increasing frequency The increasing incidence correlates with increased use of x rays in treatment of enlarged thymus tonsils and adenoids, cervical adenitis and benign pulmonary conditions The correlation suggests that irradiation around the neck in early life might be an etiologic factor in development of carcinoma of the thyroid in late childhood and adolescence

Leukemia Following Radioiodine Treatment of Hyperthyroidism is reported by E E Pochin N B Myant and B D Corbett[3] (University College London) *The association however was probably coincidental*

Woman 41 had clinical and laboratory evidence of hyperthyroidism Improvement occurred during each of three courses of thiouracil treatment but was followed by relapse No hematologic abnormality was present She received a total of 6 8 mc radioactive iodine During the following year she gained 40 lb and became asymptomatic One and a half years after receiving the radioiodine she began feeling increasingly breathless was giddy and had headaches and peripheral paresthesias Peripheral blood and bone marrow smears revealed stem cell leukemia She died two years after having received the radioiodine

Unless the leukemia was initiated in some way by irradiation within the thyroid or its capsule it is most unlikely that radioiodine treatment was relevant to the subsequent leukemia The irradiation to which the body as a whole was subjected was too low and the interval between treatment and onset of leukemia was too short to cause damage It is more likely that the leukemia was unrelated In women aged 40-45 leukemia causes 25 deaths/1 000 000 population/year One such death from leukemia should therefore arise purely by chance in 8 000 patients followed for five years

(2) J A M A 1 9 1007 1009 Nov 5 1955
(3) Brit J Radiol 9 51 35 January 1956

after radioiodine treatment assuming no association between Graves disease and leukemia

• [The danger that even small doses of radiation to the thyroid area may promote cancer still bothers many clinicians using I^{131} for treatment of hyperthyroidism The occurrence of thyroid cancer in patients subjected to minimal x ray radiation years ago is disturbing but this effect may not be comparable to the beta radiation emitted by I^{131} Further observations are needed —Ed.]

New Serum Iodine Component in Patients with Functional Carcinoma of Thyroid is reported by Jacob Robbins J E Rall and Rulon W Rawson[4] (New York) Certain carcinomas of the thyroid can concentrate iodide convert it to organic form and secrete organically bound iodine into the blood They respond to thyrotropic hormone and to goitrogens with an increased avidity for iodide In the absence of normal thyroid tissue they may maintain euthyroidism

After tracer and therapeutic doses of I^{131} were given to 23 patients with functioning carcinomas of the thyroid normal thyroglobulin thyroxin and triiodothyronine were found in the blood In addition in more than half a serum iodine component was found that differed from the products of normal thyroid metabolism It was a large molecule and appeared to be secreted by the tumor It was partly soluble in acid butanol and immobile in various chromatographic systems using butanol and resembled serum albumin It was hydrolyzed by crude pancreatic enzymes with release of a high proportion of mono iodotyrosine or thyroxin No correlation was found between presence of the abnormal serum iodine compound and various clinical and laboratory findings

Thyroxin and small amounts of triiodothyronine constitute essentially all the circulating iodine in normal and hyperthyroid persons These compounds have been demonstrated in serum of patients with functional carcinoma of the thyroid even in the absence of normal thyroid tissue Even the thyroglobulin discharged from intensively irradiated thyroid carcinoma resembles normal thyroglobulin The compound reported is apparently a functional abnormality in certain carcinomas of the thyroid

Thyroid Cancer in a General Hospital Daniel T Cloud and Charles D Branch[5] (St Francis Hosp Peoria Ill) reviewed clinical records and surgical pathology in 814 goiters

(4) J Cl F doc 1 15 1315 1331 N mbe 1955
A M A A b S g 71 366 371 S pt mb 1955

removed at thyroidectomy They concluded that cancer is a factor to be considered in treatment of nontoxic nodular goiter Cancer of the thyroid was found in none of 420 toxic but in 22 of 394 nontoxic goiters Incidence of carcinoma was *5 2% in 174 multinodular nontoxic thyroids which did not* differ significantly from the 6 9% incidence in nontoxic glands with solitary nodules Incidence of cancer in diffuse nontoxic goiters was 4 8%

Gross and Microscopic Findings in Clinically Normal Thyroid Glands in 1 000 consecutive routine postmortem examinations are presented by JD Mortensen Lewis B Woolner and Warren A Bennett[6] (Mayo Clinic) Each gland was removed in toto weighed to the neare t gram palpated intact and then sectioned in slices 2 mm thick The size number and location of all nodules were recorded and microscopically studied Of the 1 000 glands 66 were excluded because the history physical examination or laboratory tests during life revealed impaired thyroid function

The weight of the glands varied consistently with the age of the patients and there was no significant difference in the average weights of glands from men or women There was no relation between gland weight and the patient s residence whether in a goiter or a nongoiter belt

The incidence of nodularity increased with age Any discrete macroscopic lesion visually distinguished from normal thyroid parenchyma was considered a nodule Neoplasms involutional or degenerative changes discrete inflammatory lesions and scars were all considered nodules if they produced discrete localized lesions Of the clinically normal thyroid glands only 415 (50 5%) were actually non nodular 100 (12 2%) contained single nodules and 306 (37 3%) contained multiple nodules At all ages nodularity was 10 20% more frequent in females than in males The incidence of nodularity was the same for the patients in the goiter belt as for tho e in the nongoiter belt

Neoplastic and non neoplastic nodules occurred equally often Neoplasms were more frequent in females than in males in patients *over rather than under age* 40 and in patients living in goiter belts The most common nodule was the non neoplastic involutional nodule described as ade

(6) J Clin E locri 1 13 1 0 1280 Oct be 1955

nomatous colloid adenoma or degenerative regenerative this was present in about one third of all the glands and in about two thirds of the nodular ones The second most common was the true adenoma a benign usually follicular neoplasm present in about a fourth of all glands and in about half of the nodular glands In 15 glands primary occult carcinoma of low grade was seen and in 2 others a small focus of anaplastic carcinoma—a total of 4 2% of all the nodular glands and the same incidence as reported for surgically treated nodular glands

Palpation of the thyroid even with the gland in the hand of the examiner is unreliable in indicating the presence absence or the number of nodules in the gland

• [The argument about the incidence of carcinoma of the thyroid is not yet settled This study is particularly illuminating since nodularity was common in thyroid glands which were *clinically normal* and the incidence of cancer among these clinically undetectable nodules was about the same as has been reported from the same clinic in surgically removed (and therefore clinically detectable) nodules If these data are representative about 2% of the population with clinically normal thyroid glands have occult carcinoma of the thyroid Since carcinoma of the thyroid is an unusual cause of death (probably not more than 0 1%) (see 1954 55 YEAR BOOK p 604) one is forced to conclude that most of the carcinomas diagnosed by the pathologist remain in situ until the patient has died of some other disease or that the pathologist s criteria for malignancy are unrealistic in this particular tissue It seems clear that removal of a nodule diagnosed by the pathologist as malignant does not necessarily mean that the patient has been saved from death from cancer from these statistics only about one in twenty of such cancers would have produced clinically significant disease Moreover even if the surgeon removes all clinically apparent nodules he will leave inapparent nodules in 50% of the unoperated patients and cancers in 2% The wholesale excision of palpable thyroid nodules does not seem to me to be a realistic approach in preventing thyroid cancer —Ed]

Pathologic Evaluation of Radical Neck Dissection for Carcinoma of Thyroid Gland is reported by William A Meissner Bentley P Colcock and Hart Achenbach[7] (Lahey Clinic) Of the 160 patients with histologically verified thyroid cancer treated between 1949 and 1953 68 (42 5%) had radical neck dissection In general all patients with follicular or papillary carcinoma had radical dissection Radical surgery was not performed in 92 patients because in 30 the tumor was small or appeared benign in 15 pathologic diagnosis was highly malignant cancer in 11 physical condition was poor in 27 the tumor had extended too widely and operation was

[7] J Cl E doc 1 15 1432 1436 November 1955

not feasible and in 9 there were distant metastases Distant metastases and extensive local invasion occurred in all types of thyroid cancer—follicular papillary and simplex

The 68 patients with radical neck dissection had surgery whether or not cervical lymph nodes were palpable Pathologically one or more lymph nodes were involved in 44 and in 22 the tumor had invaded blood vessels Lymph node involvement and blood vessel invasion were not correlated nor was the number of lymph nodes involved in individual patients related to tumor type No relation was apparent between duration of thyroid enlargement and extent of lymph node metastases

No consistently reliable method was found for pathologically predicting from initial tumor tissue whether lymph nodes might be involved in a patient Metastases were found as frequently in papillary as in follicular cancers and no relation was found between blood vessel invasion and lymph node metastases Duration of thyroid enlargement before surgery was not reliable in predicting whether cervical nodes contained metastases At least 50% of the cancers had metastasized or showed extensive local invasion at surgery Radical neck dissection removed considerable cancer in lymph nodes In patients with only a few lymph nodes containing metastases surgery may have been truly curative Whether radical neck dissection is desirable in treating thyroid cancer can be resolved only by careful follow up of well documented cases

Results of Conservative Operations for Malignant Tumors of Thyroid George Crile Jr Julian G Suhrer Jr and John B Hazard[9] (Cleveland Clinic) believe that excellent results may be obtained by conservative operations on most papillary carcinomas of the thyroid and their follicular variants provided the primary tumor is completely excised and grossly involved groups of lymph nodes removed

Of 182 malignant tumors of the thyroid observed between 1937 and 1954 59% were papillary carcinomas Of 74 patients with papillary carcinoma who had no previous thyroid surgery 47 had metastases to regional lymph nodes at the time of surgery and four had distant metastases In this group removal of the primary tumor was associated with unilateral or bilateral removal of lymph nodes in 46 cases In 33 pa

(9) J Clin. Endocrinol. 15 142 1431 November 1955

tients previously operated on for papillary carcinoma 22 had residual tumor in the thyroid area and involvement of regional lymph nodes and 11 had involvement of regional lymph nodes without evidence of recurrence in the thyroid area Four patients had metastases to distant sites when first seen

Only 1 of the 74 patients without previous surgery died of papillary carcinoma of the thyroid with metastases to lung and bone A needle biopsy of the thyroid before surgery was believed instrumental in disseminating the tumor Five other patients died of other causes 6 months to 12 years after surgery without evidence of recurrence A sixth patient who had only cervical node biopsy because of distant metastases died of another cause 4½ years later papillary carcinoma was still present Average follow up in the other 67 patients was 4½ years An additional operation for removal of involved lymph nodes was performed in 16 patients from three months to eight years after the first operation None of these had recurrence at the site of the original operation In none were lymph nodes prophylactically removed when not grossly involved No evidence of lymph node involvement was present in 27 patients at the original surgery In only one of these was subsequent surgery necessary because of recognizable metastases to cervical nodes one year postoperatively

Of the 33 patients with previous surgery four or possibly five died as a result of the papillary carcinoma These poor results cannot be attributed to a more advanced stage of the disease Dissemination by incomplete excision of the primary tumor may have been a factor Incomplete initial operations were noted in 22 of these patients and 7 of them had distant metastases Four of them died

Eight patients with encapsulated angioinvasive carcinoma of the thyroid had definitive operations usually lobectomy Two had distant metastases when last seen and none had died Of seven with medullary carcinoma of the thyroid three had only biopsy or palliative resection and four had definitive surgery Five were dead of the carcinoma in an average of one year In 15 patients with adenocarcinoma of the thyroid the average follow up was 1½ years Definitive surgery in eight and palliation in seven has resulted in two deaths thus far Of 23 patients with undifferentiated carci

noma only 7 had definitive surgery The remaining 21 had diffuse local infiltration or distant metastases Thirteen were known to be dead of carcinoma within a few months the remaining 15 all had residual carcinoma The 11 patients with miscellaneous types of malignancy had only biopsies or palliative resections because of diffuse local infiltration or distant metastases Most survived only a few months and none beyond a year

The evidence suggests that biopsy or partial excision of papillary carcinoma often disseminates the carcinoma and renders it incurable In nonpapillary carcinomas of the thyroid the results depend on type of tumor rather than on type of treatment Radical mutilating surgery is rarely if ever indicated in treatment of thyroid carcinoma

Radioiodine Uptake in Thyroid Carcinoma was studied by R M Cunningham Gwen Hilton and E E Pochin[9] (University College London) Effectiveness of radioiodine in treatment of thyroid carcinoma depends not only on radioiodine uptake of the tumor but also on tumor sensitivity On one hand there are relatively differentiated tumors with a high radioiodine concentration but showing little change from treatment to treatment on the other hand more anaplastic tumors with a brisk and clear response to radioiodine treatment are seen although the uptake has been poor or even impossible to detect by external counting methods Of the factors of radioiodine uptake and tumor sensitivity the uptake is measurable

In 36 patients who received radioiodine treatment for histologically proved thyroid carcinoma radioiodine was demonstrated in tumor tissue in 13 and was probably present in 9 others In only two patients however was uptake clearly demonstrable before surgical or radioiodine destruction of the normal gland and it was only probable in four others at this stage It seems that a useful degree of radioiodine uptake is demonstrable after thyroid ablation in four times as many patients as show it when normal thyroid tissue is still present

It was found that thyroid carcinoma has a considerably faster radioiodine turnover than has normal thyroid tissue Using the procedure of profile counting it was observed during treatment with radioactive iodine that the uptake pro

(9) B t J R d L 8 252 56 M y 1955

gressively decreased The simplest explanation of fall in tumor uptake is that the amount of tumor tissue decreases correspondingly at each successive dose *If so this measurement* should afford a valuable criterion in control of therapy doses being given at such intervals that the tumor uptake decreases progressively until no radioiodine concentration can be detected at tumor sites A similar fall might occur however if the tumor remained constant or increased in amount but lost its powers of iodine concentration This possibility cannot be excluded

• [In addition to this article two other excellent resumes of experience with radioiodine in treatment of thyroid cancer have appeared (Beierwaltes *et al* J Michigan M Soc 55 410 1956 Kramer *et al* Brit. J Rad ol 28 307 1955) All agree that radioactive iodine therapy should be used after surgery has failed and not as a substitute for excision The prognosis is better in well differentiated tumors than in anaplastic ones but some *anaplastic tumors are unexpectedly sensitive*

No new developments in treatment of Graves disease have appeared this year but Chapman and Maloof have published an excellent summary of their experience in the use of radioactive iodine over the past 10 years (Medicine 34 261 1955) Their article is too detailed for satisfactory abstracting but is recommended for careful study by physicians interested in the field —Ed]

CARBOHYDRATE METABOLISM

Insulin I^{131} Metabolism in Human Subjects Demonstration of Insulin Binding Globulin in Circulation of Insulin Treated Subjects is reported by Solomon A Berson Rosalyn S Yalow Arthur Bauman Marcus A Rothschild and Katharina Newerly[1] (V A Hosp Bronx N Y)

In control subjects i e subjects not previously treated with insulin given insulin labeled with I^{131} intravenously the concentration of radioactivity rapidly fell in the plasma and rose in the red blood cells and urine From 2 to 25% of the radioactivity migrated with the serum proteins on electrophoresis Since pure insulin does not migrate under these circumstances the labeling procedure altered some of the insulin The larger the migrating portion the less satisfactory the preparation for studying insulin metabolism The presence of a small fraction of altered material introduces annoying complexities into experimental studies unless special *analytical methods are used*

(1) J Cl I t. 35 170 190 F bru y 1956.

noma only 7 had definitive surgery The remaining 21 had diffuse local infiltration or distant metastases Thirteen were known to be dead of carcinoma within a few months the remaining 15 all had residual carcinoma The 11 patients with miscellaneous types of malignancy had only biopsies or palliative resections because of diffuse local infiltration or distant metastases Most survived only a few months and none beyond a year

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(9) Brit J Rad 1 8 252 56 May 1955

diabetic by zone electrophoresis using starch as a supporting medium with a view to isolating the insulin neutralizing factor and localizing it in a particular serum fraction The results showed an elevation of gamma globulins No antibody to insulin could be demonstrated by conventional methods tests for both precipitin and skin sensitizing antibody giving negative reactions However electrophoretic separation of the serum showed that the insulin neutralizing activity was mainly associated with the gamma globulin fraction and that it was of the same order of magnitude as that found in the original serum Zone electrophoresis has the additional advantages over conventional methods of serum fractionation of allowing simultaneous separation of the serum into its electrophoretically separable components and direct characterization of the various components The failure to demonstrate any allergic manifestations to insulin is in accord with the previously expressed view that the insulin neutralizing factor might be due to an antibody distinct from that found in insulin allergy

• [Apparently the insulin binding gamma globulin reported by Sehon *et al* is not a specific finding in insulin resistant patients Perhaps the difference between insulin resistance and sensitivity may be partly a result of quantitative variation of the total amount of insulin binding globulin in the plasma as suggested by Berson and his co-workers

The most important development during the past year in the field of carbohydrate metabolism is the introduction of oral medications capable of lowering the blood glucose concentration of certain diabetic patients The following articles are selected to give a comprehensive view of the usefulness and of the mechanism of action of the new drugs without attempting to include all the articles which have already appeared.—Ed]

Effective Oral Antidiabetic Drug (BZ 55) In tests of a new sulfonamide derivative N_1 sulfanilyl N_2-n butyl carbamid which reaches a high level in blood with relatively small dosage development of hypoglycemia as a side effect in many cases suggested that it might be effective in diabetic therapy Ferdinand Bertram Elinor Bendfeldt and Hellmut Otto[3] (Hamburg) report a clinical trial in 82 patients with diabetes of varying severity and duration The drug was given in 0 5 Gm tablets 5 were given on the first day 3 on the second and 2 daily thereafter

BZ 55 was used as initial therapy in 28 patients aged 49 77 who had not been treated or were not taking insulin Six had previously taken insulin for a short time and one for a

(3) Deutsch med. Wchnschr 80 1455 1460 Oct. 7 1955

In animal experiments radioactivity of unaltered insulin I^{131} *in the plasma of rabbits decreased more rapidly than* that of altered insulin which moved on electrophoresis After 1 hour unaltered insulin I^{131} comprised over 50% of the total trichloroacetic acid precipitable radioactivity but after 2½ hours only 15%

Intravenous administration of insulin I^{131} to insulin *treated patients resulted in characteristically different distribution of radioactivity in electrophoretic patterns of plasma A significant fraction of the radioactivity migrated with* the front running gamma globulins (gamma₁ or beta) of the serum This insulin binding globulin appears in the plasma of human beings after they have received insulin for a few weeks It meets the definition of an antibody and reacts with insulin the antigen It retards the disappearance of insulin from the blood stream alters its migration in zone electrophoresis sediments with the globulins in the ultracentrifuge and is not a *precipitating antibody*

The clinical significance of this observation is unknown The presence of an *insulin binding globulin is not necessarily related to the degree of insulin tolerance or intolerance Fluctuations in its production may possibly be causally related to the insulin requirements in patients with so called brittle diabetes During infections which require* heightened *antibody response the increased insulin requirements so frequently observed may possibly be related to al*tered production of the *insulin transporting antibody* These possibilities represent fields for future investigation

Localization of an Insulin Neutralizing Factor by Zone Electrophoresis in a Serum of an Insulin Resistant Patient is described by A H Sehon Michael Kaye Eleanor Mc Garry and Bram Rose[2] (Montreal) The serums of some insulin resistant patients have been reported to possess insulin neutralizing activity which was attributed to an antibody *to insulin Recently* specific antibodies to insulin have been demonstrated in two insulin resistant diabetics The serums of these patients agglutinated tannic acid treated sheep erythrocytes to which insulin had been adsorbed and also lysed red cells to which the hormone had been coupled with bis diazotized benzidine

The authors fractionated the serum of an insulin resistant

(2) J Lab & Clin Med 45 65 770 May 1955

diabetic by zone electrophoresis using starch as a supporting medium with a view to isolating the insulin neutralizing factor and localizing it in a particular serum fraction The results showed an elevation of gamma globulins No antibody to insulin could be demonstrated by conventional methods tests for both precipitin and skin sensitizing antibody giving negative reactions However electrophoretic separation of the serum showed that the insulin neutralizing activity was mainly associated with the gamma globulin fraction and that it was of the same order of magnitude as that found in the original serum Zone electrophoresis has the additional advantages over conventional methods of serum fractionation of allowing simultaneous separation of the serum into its electrophoretically separable components and direct characterization of the various components The failure to demonstrate any allergic manifestations to insulin is in accord with the previously expressed view that the insulin neutralizing factor might be due to an antibody distinct from that found in insulin allergy

• [Apparently the insulin binding gamma globulin reported by Sehon *et al* is not a specific finding in insulin resistant patients Perhaps the difference between insulin resistance and sensitivity may be partly a result of quantitative variation of the total amount of insulin binding globulin in the plasma as suggested by Berson and his co workers

The most important development during the past year in the field of carbohydrate metabolism is the introduction of oral medications capable of lowering the blood glucose concentration of certain diabetic patients The following articles are selected to give a comprehensive view of the usefulness and of the mechanism of action of the new drugs without attempting to include all the articles which have already appeared —Ed]

Effective Oral Antidiabetic Drug (BZ 55) In tests of a new sulfonamide derivative N_1 sulfanilyl N n butyl carbamid which reaches a high level in blood with relatively small dosage development of hypoglycemia as a side effect in many cases suggested that it might be effective in diabetic therapy Ferdinand Bertram Elinor Bendfeldt and Hellmut Otto[3] (Hamburg) report a clinical trial in 82 patients with diabetes of varying severity and duration The drug was given in 0 5 Gm tablets 5 were given on the first day 3 on the second and 2 daily thereafter

BZ 55 was used as initial therapy in 28 patients aged 49 77 who had not been treated or were not taking insulin Six had previously taken insulin for a short time and one for a

(3) D t h m d W b h 80 1455 1460 Oct. 7 1955

long time (four years) All manifested insulin need but none had acidosis Therapeutic effect was evident in 14 patients on the first to the third day (3 5 Gm) and in 11 within 4 13 days In three the effect was so slight after 14 days even on increased doses that insulin was substituted In some cases BZ 55 could be discontinued after 10 days with no subsequent rise in blood sugar during 3 months observation as long as diet was controlled Some remained in good control for 4 months after a 10 day course others relapsed after days or weeks Many of these received a second course again with prompt effect Whether short 10 day courses intermittently or smaller maintenance doses over a long period are preferable for patients who do not get a lasting remission after the first 10 days is not yet determined

In three patients with mild acidosis without precomatose signs treatment with higher doses (to 5 Gm) over a *longer period failed to produce any effect Evidently the drug* is not suitable for treatment of acute metabolic disturbances

In 38 patients aged 41 77 who were taking insulin and some of whom had diabetes of long duration (to 30 years) insulin was withdrawn and BZ 55 substituted In 10 it was not effective and insulin had to be reinstated Although the blood sugar level sometimes increased during the first few days *the substitution was successful in 28 In some a 10 day* course resulted in prolonged remission but others needed another course of BZ 55 after a few weeks to which they again responded satisfactorily

In 10 young diabetics aged 15-40 some with newly discovered disease and some who had been treated with insulin for varying periods there was no response to BZ 55 When this drug was given *with insulin to juvenile diabetics hypo*glycemic shock developed on the first or second day

Animal experiments indicate that BZ 55 acts on the alpha cell system of the pancreas The simplest hypothesis to explain the clinical effects is that functional injury of alpha cells results in decreased production of a hyperglycemia producing substance (glucagon) antagonistic to insulin This explains *failures in juvenile diabetics* and in insulin deficient elderly diabetics who have manifest beta cell deficiency In older diabetics insulin deficiency is often only relative i e an overproduction of hyperglycemic sub

stance in alpha cells with normal insulin content of beta cells Metabolic disturbances due essentially to alpha cell hyperfunction can be influenced by BZ 55 but those due to hypofunction of beta cells remain unaffected

• [Bertram concludes that the sulfonylurea compound work by destruction of glucagon producing tissue This conclusion assumes that glucagon is diabetogenic an assumption which is strongly denied by numerous investigators (e g Van Itallie *et al* J Clin Endocr nol 15 28 1955 Elrick *et al* J Clin Invest 34 1830 1955 Bondy and Cardillo ibid 35 494 1956) It also assume that glucagon producing tissue is destroyed by the sulfonylureas This contention is refuted in the following article —Ed]

Islets of Langerhans in Diabetic Patients after Treatment with Oral Antidiabetic Drug BZ 55 showed no microscopic change in three patients studied at autopsy by H Ferner and W Runge[4] (Univ of Hamburg) There was no evidence of injury destruction or atrophy of alpha cells Findings did not differ quantitatively or qualitatively from those in diabetics not treated with BZ 55 Though no definite conclusions can be drawn from three cases they serve as orientation Review of sections in one case did not confirm the previous report on the same case by Franke and Fuchs that alpha cells were completely lacking There were no signs of atrophy or of a decrease in alpha cells This discrepancy is probably attributable to use of different histologic methods The authors used the Gomori aldehyde fuchsin method as modified by Runge and compared the results with those of the silver method of Gros Schultze The Gomori method stains granulations of alpha cells yellow orange and of beta cells intense blue violet

The theoretical mechanism of action of BZ 55 in explanation of therapeutic results assumes an effect on alpha cells with inhibition or suppression of their function Functional predominance of the alpha cell system plays a decisive pathogenic role in diabetes This hypothesis was supported by animal experiments in which oral administration of 1 3 5 Gm BZ 55/kg to rabbits caused microscopic injury of alpha cells Swelling and vacuolation and isolated instances of destruction and atrophy of alpha cells were definitely demonstrated A varying number of alpha cells were involved in individual instances the remainder being cytologically intact Though these experimental findings in animals are not interpreted as indicating conclusively the effect

(4) D t h med W h sch 81 331 333 M 9 1956

of BZ 55 on patients with diabetes they furnish the first and so far only clue to explain the mechanism involved In patients no beta cell granulation is observed indicating that increased insulin secretion is unlikely The supposition that BZ 55 acts as an enzyme inhibitor in the liver or elsewhere is plausible but so far is pure conjecture The highest doses of BZ 55 used in rabbits and rats produced no morphologic changes in the liver or kidneys

• [In addition Dr Max Miller of Cleveland informs me that experiments in his laboratory have demonstrated that these substances do not block the effects of glucagon in vivo or in vitro they do not alter the glucagon content of the pancreas and they do not change the pancreatic alpha cells —Ed]

Use of Certain Sulfonamides in Treatment of Experimental Diabetes Mellitus Personal Researches (1942-46) are reported by Auguste Loubatieres[5] (Montpellier France) The hypoglycemic action of certain sulfonamides was first observed by Janbon in 1942 when he administered p amino *benzene sulfamido isopropylthiodiazol (RP 2254) to patients with typhoid Immediate administration of glucose* aborted the symptoms of hypoglycemia but if treatment was delayed irreversible damage was done to the nervous system and death ensued

Loubatieres found that oral feeding of RP 2254 to waking fasting dogs produced prolonged hypoglycemia A dose of 0 25 Gm /kg lowered the blood sugar to 30 mg /ml The degree of hypoglycemia at least in the initial stages was a function of the blood sulfonamide level Subsequent experiments showed that the effect was abolished by total pancreatectomy but it could still be observed if a sixth of the pancreas was left in situ Similarly RP 2254 given with glucose by mouth caused a rise in the respiratory quotient which was not observed after pancreatectomy It was concluded that this sulfonamide stimulated the islets of Langerhans to secrete insulin A small dose (0 04 Gm /kg) produced a sharp fall in blood sugar when injected into the pancreatic artery A profound but perhaps slightly delayed hypoglycemia was *also observed* when RP 2254 was injected into any of the external secreting ducts of the pancreas

The part played by the pancreas was also confirmed by experiments in which the pancreaticoduodenal vein of one dog was anastomosed to the jugular vein of another pre

(5) Pres m d 63 1701 1703 D 10 19 5

viously made diabetic with alloxan The action did not seem explicable in terms of inhibition of diabetogenic hormone since the hypoglycemia induced by RP 2254 could not be prevented by simultaneous administration of diabetogenic extract from the anterior pituitary By 1946 Loubatieres felt that he could advocate the trial of RP 2254 in human diabetics

Studies on other related compounds to establish what part of the molecule was responsible for the hypoglycemic effect showed that the tertiobutyl and isobutyl derivatives were the most active

• [It is interesting to realize that the basic observation from which the antidiabetic sulfonylureas have developed were made by Loubatieres and his colleagues more than 14 years ago—Ed]

Inhibition of Insulinase by Hypoglycemic Sulfonamides was investigated by I Arthur Mirsky Gladys Perisutti and Daniel Diengott[6] (Univ of Pittsburgh) The new sulfonamide BZ 55 has been reported to lower the blood sugar of normal animals and of many patients with diabetes mellitus but the mechanism has not been clear Two arylsulfonyl ureas fed to normal male rats were found to be potent hypoglycemic agents and also decreased the insulinase activity of the livers considerably within one hour of administration

Insulinase activity can be inhibited by a variety of heavy metals and such sulfhydryl poisons as iodoacetate and p chlormercurobenzoate These arylsulfonylureas are non competitive inhibitors of insulinase

The study suggests that the hypoglycemic action of the sulfonamides is due to noncompetitive inhibition of insulinase and decreased destruction of endogenous insulin The fact that the sulfonamides are effective in some patients with diabetes mellitus and the results of this study support the hypothesis that insulinase activity may be increased to account for insulin deficiency in diabetes mellitus

• [This interpretation of the action of antidiabetic sulfonylureas seems more consonant with present understanding of carbohydrate metabolism than the glucagon hypothesis of Bertram Moorhouse and Kark (Clin Res Proc 4 124 1956) however have suggested that these substances may act by reducing the rate of release of glucose by the diabetic liver At present the exact mechanism of action is not clear

In addition to Bertram a number of others have recorded their experience with the new drug All agree that it is successful in most instances but that a certain number of patients especially juvenile diabetics are

(6) M t bol m 5 156 161 M h 1956

unresponsive It is useless in the treatment of diabetic acidosis The recommended dose schedules range from 1 to 4 Gm /day orally Some authors attempt to maintain a sulfonamide blood level of about 10 mg /100 cc Since the substances can produce serious hypoglycemia they must be used with the same precautions as insulin Although good results are widely reported on the basis of a few months of treatment only prolonged observation will tell whether these substances like other sulfonamides are capable of producing late toxic reactions such as periarteritis nodosa leukopenia and other sensitivity reactions —Ed]

Functioning Metastases from Islet Cell Tumor of Pancreas Conrad J Baumgartner and John L Reynolds[7] (St Vincent s Hosp Los Angeles) state that only about 10% of islet cell tumors are frankly malignant and about half of these will have functioning metastases Control of the hypoglycemia in such situations not amenable to surgery is difficult as seen in the following case

Woman 59 had dizzy spells for many years During hysterectomy for a fibroid the abdomen was examined and a hard irregular sized tumor was felt in the region of the tail of the pancreas The fasting blood sugar level on the fifth postoperative day was 108 mg /100 ml Two weeks later the tumor was removed. Histologic study revealed islet cell carcinoma and metastases to lymph nodes

The patient remained asymptomatic for several months but later *episodes of vertigo and nausea returned When diplopia developed she* was rehospitalized On examination she appeared very nervous and had a tremor An irregular liver edge was palpable 4 fingerbreadths below the costal margin Blood sugar was 33 mg /100 ml and symptoms were promptly relieved with glucose intravenously

Exploration of the abdomen revealed no evidence of local recurrence but the liver was studded with nodules of islet cell carcinoma with essentially the same cell type as the original tumor For about a month she did well on a high fat high protein diet with between meal feedings and a feeding at 2 a m but when she again had a severe attack of hypoglycemia ACTH gel was started She received 40 units daily for a week together with potassium chloride by mouth and a restricted sodium intake When dramatic relief took place ACTH was gradually reduced to 40 units every third day on which she remained well controlled

The role of corticotropin is not clearly understood While many authors have observed beneficial effects from steroids in controlling hypoglycemia due to islet cell tumors others have doubted their efficacy

In discussion C W McLaughlin reported on a similar patient who also had islet cell metastases in the liver and frequent attacks of hypoglycemia On home care however the attacks became less frequent and could be controlled by

(7) A M A Arch S g 70 793 800 J n 1955

taking large quantities of reinforced fruit juice There is no explanation for the dramatic remission without therapy

• [We have recently seen a patient with malignant insulinoma whose hypoglycemia was not controlled by cortisone but who seemed to respond temporarily to hydrocortisone Gershberg and Ralli (Am J Med 20 651 1956) described a similar patient controlled for three years by cortisone In this desperate situation the steroids should be tried if one proves inadequate another may help —Ed]

Familial Hypoglycemia Precipitated by Amino Acids Spontaneous hypoglycemia a reflection of abnormal carbohydrate metabolism may be caused by a variety of diseases W A Cochrane W W Payne M J Simpkiss and L I Woolf[8] (Hosp for Sick Children London) report three cases in one family and another unrelated case in which convulsions and profound hypoglycemia were induced by administering proteins or amino acids.

CASE 2—Girl aged 2/ months developed normally until two weeks before admission At that time she was changed from breast feedings to full cream dried cow s milk feedings When extra sugar was omitted from the feedings she began having generalized convulsions became flushed sweated and lost consciousness Results of physical and neurologic examination were normal The only abnormal laboratory findings were fasting blood sugar levels between 32 and 50 mg /100 ml just before meals the blood sugar levels ranged from 40 to 65 mg The cerebrospinal fluid sugar level was 25 mg / 100 ml

Laparotomy was performed The pancreas was normal grossly and histologically She was discharged on a normal mixed feeding schedule with only an eight hour fast at night During the next year she had seizures at about three month intervals She sat up at age 10 months walked at 1 year and began talking at 20 months

CASE 3—Man 27 father of the children in Cases 1 and 2 (Case 1 was similar to Case 2) had fits as a baby From age 10 months to 13 years he occasionally went into a deep sleep which lasted a few moments to four days Since then he has been well Fasting blood sugars on three occasions were 64 46 and 48 5 mg /100 ml

Epinephrine was given subcutaneously after an eight hour fast to three patients (Cases 1 2 and 4) The blood sugar level increased in the first half hour from 27 to 45 mg /100 ml 45 140 mg and 52 115 mg respectively the level was still elevated two hours later Glucagon given to two patients increased the blood sugar for the first half hour but control levels were reached by two hours Cortisone was given to one patient for eight months no seizures occurred during this period Fasting blood sugars which had been 17 50 mg /100 ml increased to 40 61 mg and blood sugar

(8) J Cl I t 35 411 422 Ap 1 1956

levels before feedings, previously 35-45 mg, rose to 75 107 mg

Casein feeding had a marked hypoglycemic effect on three patients (Fig 110) but no such effect on normal subjects Blood amino acids rose similarly in both groups the peak coinciding with the minimal blood sugar concentration Gelatin fed to one patient had a slight hypoglycemic effect

Other clinicians have referred to a special group of pa

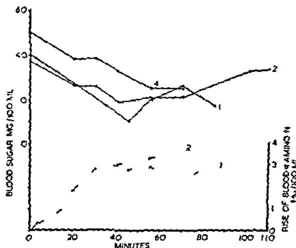
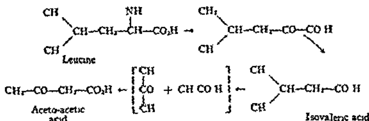


Fig 110—Blood sugar (continuous l) d min n troge e (br k lin) Cases 1 2 and 4 after as fed g 14 Gm (1 5 Gm /kg body weight) er 25 minutes n Case 1 16 Gm. (1 5 Gm /kg) ove 10 m n te n Ca and 24 Gm (1 5 Gm /kg) o e 10 m ut n C s 4 (Courtesy of Cochrane W A et al J Clin Invest 35 411-4 April 1956)

tients with infantile idiopathic hypoglycemosis in whom age at onset of symptoms and findings were similar to the familial group described here A high protein low carbohydrate diet has been suggested for treatment of idiopathic functional hypoglycemia but in two cases in the literature such diets made the patients worse In the authors patients protein feeding was clearly the cause of hypoglycemia A most dramatic effect was obtained with l leucine The effects of test doses of casein and gelatin could be fully accounted for by their leucine content Normal subjects did not react in the same manner

l Leucine is metabolized according to the following scheme



The keto acid formed from leucine by transamination is not readily available Isovaleric acid is split in vivo to a 3 carbon and a 2 carbon fragment each giving rise to acetoacetic acid Acetoacetic acid cannot be the active substance since it is formed by tyrosine which has no hypoglycemic effect Hence isovaleric acid is the only readily available metabolite of leucine that might have a hypoglycemic effect A test dose of commercial isovaleric acid produced as profound a hypoglycemia as did an equivalent dose of leucine Since a larger dose of isovaleric acid had no effect on the blood sugar concentration of a normal subject it is most likely that the acid is the true hypoglycemic factor in these four patients and that leucine acts by virtue of its rapid conversion to isovaleric acid

* [These observations are of great practical importance since the usual dietary therapy for spontaneous hypoglycemia is a high protein low carbohydrate diet If a patient so treated becomes worse rather than better the possibility that he may have leucine induced hypoglycemia must be considered —Ed]

Blood Sugar Levels Following Intravenous Infusion of Glucose and Fructose in Adults were investigated by J C Peden Jr J S Riley L Bond and R Elman[9] (St Louis) Each of six subjects was given an intravenous infusion of 1 000 ml of 10% glucose in water over 90 minutes followed the next day by a similar amount of 10% fructose at the same rate In another six subjects order of infusion was reversed Blood sugar determinations by the Somogyi method were made on venous samples before and after infusion and at one two and three hours thereafter All patients fasted

Whereas higher blood sugar levels were found during infusions of glucose compared with fructose postinfusion levels were just the reverse This phenomenon is apparently due

(9) Metabol in 4 318 322 J ly 1955

to the fact that removal of glucose from the blood stream requires phosphorylation under the influence of insulin The process is not as rapid as in the case of fructose which may be transferred across the cell wall in a free state The great stimulus to elaboration of insulin under the influence of the high blood sugar levels after glucose infusion apparently continues after the infusion most likely accounting for the low postinfusion blood sugar levels usually below fasting and occasionally as in one of the subjects accompanied by symptoms of hypoglycemia

Similar observations have been made with fructose orally which produces only a slight rise in the total blood sugar value with no later fall below fasting values This suggests that fructose may represent a more desirable carbohydrate for infusion and oral intake in patients with hypoglycemic tendencies

Insulin Edema Report of Case Generalized edema following insulin administration as it developed in a patient reported by Arthur H Griep[1] (Evansville Ind) is relatively rare Insulin allergy in general may occur in atopic or non atopic person Hypersensitivity reactions to insulin vary from slight local induration to generalized reactions and are most often due to the insulin molecule and not the protein of the species from which it is obtained Antihistaminics are valuable in treating insulin hypersensitivity It is stressed[1] that insulin allergy and insulin resistance are not the same immunologic process

Woman 27 was hospitalized with symptoms and signs of diabetic acidosis Diabetes came well under control within eight days and 50 units of U80 NPH insulin (iletin®) daily with proper diet was prescribed

Two days later anasarca set in and progressed accompanied by arthralgia headache blurring of vision shortness of breath with minimal wheezing and abdominal distention Local induration developed at site of all insulin injections Examination revealed massive edema of the upper and lower extremities with marked facial and retinal edema and ascites No definite urticarial lesions were noted Results of urine examination were negative The blood nonprotein nitrogen level was 33 mg /100 ml Blood values showed moderate hemodilution the differential count was normal and eosinophilia was absent The fasting blood sugar level was 185 mg /100 ml Results of intradermal tests with U40 regular insulin (iletin®) were negative Continuation of the same diabetic regimen but with no salt in the diet and with diuretics resulted in rapid diuresis She remained edema

(1) J I d ana M A 48 872 873 A g t, 1955

tree but continued to have local induration at the site of the NIH insulin injections

Antihistamines were not used Whether edema would have subsided spontaneously or whether salt restriction and diuretics were of benefit remains unknown

Use of Hormones in Management of Pregnancy in Diabetes with special reference to fetal mortality is discussed in a report to the Medical Research Council by their Conference on Diabetes and Pregnancy [2] Comparable groups of patients with diabetes but free from major cardiovascular complications attending nine hospitals were classified by age and parity and randomly divided into hormone treated and non hormone treated groups One group received tablets containing graduated doses of ethisterone (25 250 mg daily) and stilbestrol (50 200 mg daily) the others were given inert tablets In all other respects the management of pregnancy was the same All patients 76 hormone treated and 71 non hormone treated were followed for at least six months after delivery

Frequency of stillbirth and neonatal death in the two groups was almost the same with total death rate of viable fetuses 24% in the hormone treated group and 26% in the other Birth weights were on the average equal Four congenital malformations occurred in the treated group and seven among controls frequency of malformation associated with fetal loss was however the same being three in each group

Diabetic control during pregnancy was equally good in the two series and incidence of hydramnios edema and albuminuria was equal No significant excess in incidence of toxemia was noted in the non hormone treated group and the trends in blood pressure readings during pregnancy were identical

It is concluded that stilbestrol and ethisterone in these oral doses do not reduce fetal mortality in diabetic patients and have little if any beneficial effect on maternal health in pregnancy

The So called Prediabetic Syndrome of Pregnancy The syndrome includes obstetric complications (toxemia fetal giantism prematurity fetal or neonatal mortality) diabetic heredity and maternal obesity in women who later have

(2) Lancet 2 833 836 Oct 22 1955

diabetes Correlation between fetal giantism and subsequent diabetes is especially high J Pirart[3] (Univ of Brussels) studied 502 women who gave birth to 1 420 viable children in a prediabetic period

In comparing prediabetic women with those who did not develop diabetes no differences were found in the rates of toxemia prematurity intrauterine death natal and neonatal death or total perinatal mortality The figures were comparable to those found in normal populations Fetal giantism however was common More than one child in four and more than one mother in three was so affected in the prediabetic group Repetition of fetal giantism was common in the same sibship The complete prediabetic syndrome was found in only a small group of women who had a dramatic succession of obstetric incidents Considering the main component only fetal giantism the syndrome is fairly common While all the components are rarely present their association with fetal giantism supports the concept of a true prediabetic syndrome

The syndrome is not progressive The incidence of fetal giantism does not increase during the 30 year period before diabetes appears and there is no close correlation between fetal giantism and the later occurrence of diabetes in the mother also the incidence is not different in prediabetic mothers whether or not diabetic heredity is present In normal mothers diabetic heredity is associated with a higher incidence of large babies Diabetic heredity therefore is more important than the actual development of diabetes

A genetic predisposition to bear overweight babies independent of diabetic heredity is present in nondiabetic and diabetic mothers and fetal giantism is closely related to the mother s obesity *In decreasing importance the factors associated* with fetal giantism are heredity mother s obesity diabetic heredity and the subsequent development of maternal diabetes

Complications of Diabetes Mellitus were studied in 103 patients by Perry S MacNeal and John Rogers[4] (Philadelphia) *with reference* to duration and severity of diabetes race age and sex and degree of diabetic control Most pa-

(3) A t doc 1 20 19 08 1955
(4) M Cl N rth Ame ca 39 1607 16 9 N vembe 1955

tients were indigent with little education 55% were Negro and 86% were over age 50 74 were females

Incidence of cataracts was increased in elderly patients and in those with diabetes for over 15 years It seemed to be influenced neither by severity of disease as judged by presence or absence of weight loss with polyuria nor by degree of diabetic control as judged by blood sugar and urinalysis Senile cataracts apparently occur earlier in diabetics than in normal persons Diabetic retinopathy was present in 53% of patients No evidence was noted that good control altered incidence of retinopathy but retinopathy tended to be more severe in the poorly controlled group

Systolic hypertension alone occurred in 29% of the entire group more frequently in the obese and those with long standing diabetes Significant systolic and diastolic hypertension was seen in 19% Heart disease of some degree was detected in 57% Degree of diabetic control did not alter incidence of hypertension or cardiac disease

Albuminuria was present in only 8% Renal excretion of phenolsulfonphthalein was impaired in 12% Renal damage seemed more frequent in patients described as very poorly controlled the good and fair groups fared almost as well as the perfect group with respect to renal complications

Peripheral vascular disease was detected in 32% of the entire group with higher incidence in those with diabetes for 10 15 years (56%) in those in whom disease had begun without weight loss (43%) or without polyuria (48%) and in those moderately obese at onset of diabetes Patients with poor diabetic control fared slightly worse than patients with good control

Neuropathy (loss of vibratory sense absent reflexes) was present in only 7% No gross neuropathy occurred in poorly controlled patients the highest incidence being in the perfectly and well controlled groups

Control of Diabetes Eleanor Giffin and Joseph B Cortesi[5] (Ellis Hosp New York) studied 46 patients aged 7 42 who had diabetes for 5 28 years with onset before age 20 In over two thirds of the group diabetes had developed before age 15 and 65% had had diabetes 10 years or longer There were 20 men and 26 women showing that only in diabetes

(5) N w Y k J Med 55 1858 1863 J 1 1 1955

of middle age does dominance of the female sex really become manifest A known family history of diabetes was present in 69% The authors tried to correlate the degree of control of diabetes with development of degenerative lesions in the kidney retinas and blood vessels and of other complications

Control of diabetes was excellent in 2 patients good in 7, fair in 6 and poor in 31 (68%) Of those with excellent or good control five had diabetes for 5 10 years two for 15 20 and two for over 20 years None of them took less than 30 units of insulin daily

X rays revealed evidence of vascular calcification in six patients five of whom were poorly controlled No relation was found between control of diabetes and capillary fragility *but duration of diabetes may be of some importance* All but 1 of 11 patients who had ECG changes fell into the poor control group There was a high incidence of coronary artery disease Seven patients had hypertension even in the first 10 years of the disease Abnormal ballistocardiograms were seen in 27 patients (58%) Nephropathy was present only in the poor control group *Two patients with nephropathy who* died needed much less insulin preterminally Retinal changes were seen in 65% of the poor control group and in 20% with fair or good control There were no retinal changes in two patients under excellent control and only grade I retinopathy was found in fair and good control groups

Four poorly controlled patients had an enlarged heart on x rays No hepatomegaly was found in the entire group One patient had arrested tuberculosis and one hyperthyroidism

This study shows that control is more important than duration or severity of the diabetic state in preventing degenerative lesions The large percentage of patients in the poor control group indicates that young diabetics have not been so well controlled as is desirable

• [It is difficult to understand why various observers differ so radically as to the importance of *close* control of diabetes in preventing the development of vascular and neuropathic complications The fact that retinopathy may be present when diabetes is first recognized seems strong evidence that prolonged lack of diabetic control is not of major importance in the development of this complication *The problem is discussed in the next paper* —Ed]

Diabetic Retinopathy in Newly Diagnosed Diabetes Mellitus Most ophthalmologists have had occasion to diagnose

diabetes mellitus ophthalmoscopically in patients who deny having noted diabetic symptoms Incidence of diabetic retinopathy in newly diagnosed diabetes mellitus varies in different series but in some recent reports is surprisingly high as much as 14 and 15% To investigate the relation of retinal angiopathy to recent diabetes Knud Lundbaek[6] (Aarhus Denmark) studied in detail 246 patients with diabetes newly diagnosed during the years 1945 54 in whom ophthalmoscopic examination was done Retinopathy was present in 10 or 4 1%

Special attention was paid to evaluation of accuracy and details of case histories The low incidence of retinopathy in newly diagnosed diabetes mellitus in this series supports the theory that diabetic angiopathy is a long term diabetic manifestation Study of the 10 patients presenting diabetic retinopathy at the time diabetes was diagnosed revealed that in five the disease might easily have existed for decades and in three others a duration of some years seemed probable This left only two in whom no explanation for early appearance of diabetic retinopathy was evident i e less than 1% It is noteworthy that all 10 patients were over 40 and that none had severe diabetes

It must be concluded that diabetic retinopathy in recent diabetes mellitus if it occurs at all is rare

Peripheral Arteriosclerotic Vascular Disease in Diabetics Results from Lumbar Sympathectomy and Comparative Analysis with Nondiabetic Patients There is a definite association between the diabetic state and incidence of clinically significant arteriosclerotic peripheral vascular disease Of 275 patients with arteriosclerosis obliterans undergoing lumbar sympathectomy during the years 1945 52 at the University of Michigan Hospital 93 (33 9%) had clinically proved diabetes Robert E L Berry and C Thomas Flotte[7] (Univ of Michigan) compared the results following operation in these patients with those observed in 182 nondiabetic patients

In the absence of ulceration or gangrene results in nondiabetics were somewhat better than in diabetics After necrosis had developed results were essentially the same

Below age 55 48% of diabetics obtained a good result

(6) A ta m d d na 152 53 60 1955
(7) A M A A h S g 71 460 467 S p mbe 1955

Above 65 only 12% were benefited The results in diabetics over 65 with significant elevation of blood pressure or central nervous system or cardiac involvement were so poor that they represented a contraindication to sympathectomy

Severity duration or adequacy of treatment of diabetes *little affects the percentage of good results obtained* The amputation rate is higher in inadequately treated and in short term diabetics

Although sclerosis of the larger arteries of the lower extremities is of paramount importance in development of peripheral ischemia increasing emphasis has been placed on the characteristic lesions which now seem specific for diabetes in arterioles venules and capillaries

An increase of blood cholesterol is lacking in many diabetic patients who have marked lipid deposition It would seem therefore that instability of cholesterol rather than increased concentration is more essential to lipid accumulation

Steatorrhea Complicating Diabetes Mellitus with Neuropathy Report of Cases Without Apparent External Pancreatic Insufficiency Gastric atony and dilatation postprandial abdominal cramping severe constipation and intractable diarrhea with watery stools nocturnal exacerbations and fecal incontinence associated with diabetes mellitus are attributed to altered gastrointestinal motility due to visceral diabetic neuropathy Kenneth G Berge Eric E Wollaeger Donald A Scholz E Douglas Rooke and Randall G Sprague[8] (*Mayo Clinic*) *report on six patients with diabetes mellitus* neuropathy diarrhea and steatorrhea None had any evidence of external pancreatic insufficiency

Diabetes preceded the gastrointestinal symptoms by an average of seven and a minimum of two years Three patients had diabetic retinopathy and two nephropathy with renal insufficiency Altered sweating patterns postural hypotension impotence vesical dysfunction and pupillary abnormalities indicated widespread autonomic neuropathy None of the patients had bulky malodorous stools but laboratory evidence of steatorrhea was striking With dietary fat intakes *of 96 145 Gm daily fecal fat ranged from 14 to 70* Gm daily With this intake normal subjects excrete *7 5 Gm* or less daily

(8) Diabetes 5 531 Jan Feb 1956

Diarrhea was not alleviated with pancreatin banthine® atropine vitamins cortisone or parenteral liver extract in three patients steatorrhea and azotorrhea increased while they were taking banthine®

The clinical picture was not that of external pancreatic insufficiency and there was no evidence of nontropical sprue Whipple's disease or enteroenteric fistulas or anastomoses Large quantities of pancreatic enzymes were demonstrated in the duodenum of two patients in whom the test was completed Indirect evidence against the existence of pancreatic insufficiency was the lack of abdominal pain suggestive of pancreatitis absence of pancreatic calcification on x ray severe degree of diabetes and the long interval by which the diabetes antedated the development of diarrhea

Diagnosis and Treatment of Acute Pyelonephritis in Diabetes Mellitus are reported in 23 patients by Guy E Joron A F Fowler Joan de Vries Grant Reid and W H Mathews[9] (Montreal) Pyelonephritis a common and serious complication of diabetes mellitus at autopsy is found about six times oftener in patients with than in those without diabetes The characteristic nephropathy of long standing diabetes is a mixed lesion of arteriolosclerosis hyaline deposits and some degree of pyelonephritis Often acute pyelonephritis clinically unsuspected is the principal cause of death The usual signs and symptoms of acute pyelonephritis apparently do not always become manifest in patients with diabetes

The most common and serious form encountered in patients with diabetes does not show the classic picture of chills rigors acute loin pain and tenderness in the costovertebral angle high spiking fever and burning urination If the condition is untreated death occurs within a week or two

Commonest presenting complaints were nausea and vomiting Other systemic symptoms in order of frequency were fever and chills delirium and confusion drowsiness and weakness Pain was never prominent or acute and only three patients mentioned loin pain Urinary symptoms were not striking and when they occurred were usually attributed by the patient or physician to poor control of diabetes Physical examination disclosed tenderness in the loin in only two pa

(9) C d M A J 73 956-958 De 15 1955

tients The patients usually looked seriously ill despite paucity of physical signs

Pyuria was not always present In all patients the urine contained an abnormal number of pus cells on at least one occasion but in a fourth of the patients pyuria was not found on first examination A catheterized specimen of urine should be cultured if the diagnosis is suspected

Common mistaken diagnoses are diabetic acidosis cerebrovascular lesion and surgical intra abdominal lesion or the diagnosis is not suspected because pus is not found in the urine

Pain was not localized and never severe Why the pain should more often be located anteriorly and never in the costovertebral angle is unknown Intestinal obstruction cholecystitis and diverticulitis were often suggested by the symptoms Occasionally it may be impossible to distinguish *acute pyelonephritis from an acute surgical intra abdominal* lesion

Glycogen Storage in Liver in Diabetes Mellitus In a diabetic clinic of 800 patients R Winston Evans T R Littler and H S Pemberton[1] (Liverpool) observed a new syndrome in four patients aged 13 25 This syndrome occurring in patients with severe or brittle diabetes is characterized by a constant tendency to hypoglycemia while taking insulin *and by an enlarged liver which on biopsy is distended* with masses of glycogen as in von Gierke s disease though other signs of this disease are absent In a series of 50 diabetics with homologous serum jaundice liver biopsy was done during the acute phase and one or two years later and no comparable amounts of glycogen were found The discrepancy between glycogen rich liver and hypoglycemic tendency and the inability to mobilize the excess liver glycogen by administering glucagon to the study patients suggest that for some unknown reason glycogenolysis is impaired in these patients The accumulation of glycogen may have resulted from prolonged periods of hyperglycemia

The syndrome is well illustrated by the history of the following patient

Woman age 25 had had diabetes since 13 which was always difficult to stabilize due to recurrent attacks of hypoglycemia She was hospitalized because of recurrent swelling of the parotid glands re

(1) J Cl Path 8 110 113 May 1955

peated attacks of hypoglycemia and amenorrhea While in the hospital she noticed increasing abdominal distention Examination revealed a smooth soft enlargement of the liver 3 fingerbreadths below the right costal margin Biopsy showed hepatic cells distended with glycogen The parotid glands had fluctuated in size up to the present time and there appeared to be some relation to the hypoglycemic attacks

The diabetes was brittle with a morning fasting blood sugar level of 500 mg /100 ml and typical hypoglycemia in the afternoon Abdominal exploration confirmed the smooth enlargement of the liver Although the pancreas was grossly normal the islets were small and scanty

CALCIUM PHOSPHORUS AND THE PARATHYROID GLANDS

Comparative Study of Some Effects of Administration of Dihydrotachysterol and Calciferol to Rats was done by Roy V Talmage and B F Dodds (Rice Inst) McLean has found that dihydrotachysterol (A T 10) and vitamin D (calciferol) are equally effective in maintaining near normal serum calcium levels in hypoparathyroidism though calciferol requires a dose about double that of A T 10 The authors studied the influence of both dihydrotachysterol and calciferol on calcium and phosphate serum levels and on the progressive excretory changes of these two ions following parathyroidectomy

In the experiments A T 10 was effective only orally at the dose levels used In normal rats it raised the serum calcium level from 10 6 to 13 1 mg /100 ml and the renal calcium excretion from 0 2 to 0 39 mg /hour However only minor increases in phosphate excretion were produced When given before parathyroidectomy A T 10 prevented the fall in serum calcium but did not prevent the temporary increase in renal calcium excretion that follows the loss of circulating hormone Conversely while the drug was able to prevent the fall in renal phosphate excretion it was unable to prevent the rise in serum phosphate levels that follows removal of these glands When the drug was given at the time of or following parathyroidectomy it raised the renal calcium excretion from 0 4 mg /hour in the control animal to 0 21 mg / hour in the test animal and the serum calcium from 7 6 to

(2) E doc 1 gy 57 236-242 A gu t 1955

12 2 mg /100 ml I or the most part vitamin D could not be shown to influence the physiologic functions studied in these experiments The only possible effects seen were minor increases in renal calcium excretion and a light retardation in the fall in serum calcium following parathyroidectomy Since these experiments were run with animals maintained for 10 days before the experiment on a calcium free diet ef fects on , ut absorption of calcium were minimized

It appears from the data presented that the action of A T 10 in rats is restricted almost entirely to its ability to remove calcium and phosphate from bone

Induced Hypercalcuria Dynamic Test for Skeletal Inves tigation is reported by A Lichtwitz S de Seze D Hioco and Ph Bordier[3] (Paris) Intravenous injections of 176 mg

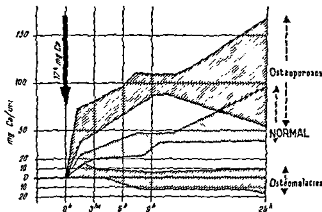


Fig 111 —Appea c f pr je t f th ee type of d ced hyp al u a All curves beg n t O (C urt y f L htw t A t al Sema ne hop Pa 31 3 89 3793 D 2 1955)

calcium were given over about five minutes to normal sub jects and patients with metabolic bone disease Urine was collected and calcium excretion measured 3 9 and 24 hours after injection (Fig 111) and compared with output at the same time on the preceding day During these two days the patients were not given milk cheese or eggs

In the seven normal subjects the percentage of adminis tered dose excreted at 3 hours ranged from 7 to 23 at 9 hours from 21 to 48 and at 24 hours from 23 to 73 Among

(3) Sem n hop Pa s 31 3789 3793 D c 2 1955

eight patients with osteomalacia less than 10% of the dose had been excreted at 3 hours and virtually no more was excreted in the next 18 hours Six patients with osteoporosis excreted 15 52% in the first 3 hours 37-61% during the next 6 hours and 50 108% during 24 hours except one patient who appeared to retain calcium between 9 and 24 hours Four patients shown by biopsy to have both osteomalacia and osteoporosis excreted 5 10% at 3 hours 10 18% at 9 hours and 11 45% in 24 hours

Multiple Myelomatosis Simulating Hyperparathyroidism Mary G McGeown and D A D Montgomery[4] (Queen s Univ Belfast) report a case

Woman 46 had polydypsia and polyuria for six years Three weeks before hospitalization she had sudden sharp sternal pain followed by vomiting three or four times daily X ray examination revealed a double fracture of the sternum and moderate demineralization of vertebral column and ribs consistent with diagnosis of hyperparathyroidism Levels of serum calcium ranged between 12 9 and 19 1 mg /100 ml of serum phosphorus between 3 2 and 5 9 mg and of alkaline phosphatase between 9 and 11 King Armstrong units Urinary clearance tests revealed decreased tubular reabsorption of pho phate Albuminuria was present but no Bence Jones protein On a low calcium diet excretion of calcium remained two to three times normal

With these findings diagnosis of hyperparathyroidism seemed positive The neck was explored and three parathyroid glands removed The e contained a large amount of fatty tissue the chief cells were normal and there was no evidence of excess activity She did well for 24 hours but suddenly became pale and cyanotic and died on the fourth postoperative day despite vigorous therapy

At autopsy the fourth parathyroid gland was normal Bone marrow was normal in most areas but in several places was replaced by myeloma cells A stored specimen of blood was found to contain 9 6 Gm / 100 ml protein with albumin 3 3 Gm and globulin 6 3 Gm Electrophoresis showed a sharp peak in the beta globulin which made up 59 5% of the total protein

• [The differentiation of multiple myeloma from hyperparathyroidism may often be difficult Thi case was particularly misleading because tubular phosphate reabsorption was reduced and dietary calcium restriction failed to reduce hypercalcuria These are usually considered specific tests of increased parathyroid function but may be confusing if hypercalcemia has produced impa red renal function —Ed]

Postoperative Hypoparathyroidism In the experience of Joseph A Buckwalter Robert T Soper Jack Davies and Edward F Mason[5] (State Univ of Iowa) permanent parathyroid deficiency following thyroid surgery is not infrequent

(4) B t M J 1 86-88 J 14 1956
(5) S g Gynec & Obst 101 657-666 Dec mber 1955

management is often difficult and complications are not uncommon even when the patients are under medical surveillance Their report concerns 50 cases of surgically induced hypoparathyroidism seen since 1927

The onset of clinical hypoparathyroidism occurred most often in the week following operation Tingling paresthesias and numbness of the fingers and toes were most common Carpopedal spasm Trousseau s Chvostek s and Erb s signs soon appeared Tightness and stiffness of other muscle groups a feeling of restricted inspiration and expiration hyperventilation and laryngospasm were less frequent and late Of the 50 patients 33 had Chvostek s sign 30 tingling 29 muscle cramps 23 carpal spasm 23 Trousseau s sign 20 pedal spasm 14 numbness 9 paresthesias 8 stiffness 6 each disorientation or twitching 5 convulsions 4 ringing in ears 3 each hyperventilation or Erb s sign and 2 each laryngospasm dysphagia or anxiousness

Vitamin D 50 000 200 000 units daily and calcium orally (calcium lactate powder 5 15 Gm daily) should be started as soon as diagnosis is made The correct doses are determined by following the patient s course and serum calcium and phosphorus levels Vitamin D is available in 50 000 unit capsules the dose is 1-4 capsules daily orally its cost is $0 03 0 12 cents daily and it is effective when used with increased calcium and decreased phosphorus intake Calcium lactate powder provides the high calcium intake 1 teaspoon equals 3 Gm dosage is 1 teaspoon three times daily and at bedtime in drinks other than milk its cost is $0 008 daily and it has the advantage of providing high calcium ingestion for absorption and for combining with phosphorus as insoluble $Ca_3(PO_4)$ which is lost in the stool thus maintaining a low serum P

Late complications in the 50 patients with postoperative hypoparathyroidism were cataract in 10 convulsions in 7 mental deterioration in 3 psychosis in 2 and cardiac insufficiency and death in 1 each

In a patient who has recently had thyroid surgery the appearance of these symptoms and signs is pathognomonic of parathyroid insufficiency Laboratory determinations showing depressed serum calcium and elevated serum phosphorus levels and decreased or absent calcium excretion in the urine confirm the diagnosis Further confirmatio s pro

vided by the prompt disappearance of symptoms when calcium is administered intravenously Prompt adequate therapy may prevent progression to late irreversible sequelae of cataract convulsions mental disorders or death

• [Note the small number of patients with positive Chvostek s and Trousseau s signs The possibility of hypoparathyroidism should be considered in any patient having thyroid surgery even if the usual diagnostic signs are absent —Ed]

Insensitivity to Vitamin D Developing during Treatment of Postoperative Tetany Its Specificity as regards Form of Vitamin D Taken Four patients with chronic hypocalcemic tetany due to accidental removal of parathyroid glands who showed increasing insensitivity to calciferol (vitamin D) though previously symptom free and normocalcemic on smaller doses are described by C E Dent Christine M Harper Margaret E Morgans G R Philpot and W R Trotter[6] (University College Hosp London)

When the same or smaller doses of A T 10 (in three patients) or vitamin D_3 (in one patient) were substituted for calciferol symptoms of tetany were quickly relieved and plasma calcium level rose to normal All four patients were well maintained on small doses of the substituted preparation

In two patients calcium balance and other data at the time of change in vitamin D preparation showed that in the phase of insensitivity to vitamin D neither responded to the action of large doses of calciferol When the form of vitamin D was changed all the actions of the vitamin were immediately manifest—improved absorption of calcium from the intestine decreased renal threshold for calcium raised plasma calcium levels and in one rise in plasma calcium level preceded changes in calcium absorption sufficient in themselves to produce such rises These were offset by the approximately equal rise in urinary calcium level hence the over all calcium balance remained unchanged due to the direct action of vitamin D on bone

All the evidence suggests that the patients had previously been sensitive to calciferol in small doses and had become completely insensitive to it even in large doses but that insensitivity was to calciferol alone and not to normal doses of the closely related substances A T 10 and vitamin D_3 This phenomenon is likely to have some bearing on the

(6) Lancet 2 687 690 Oct 1 1955

management is often difficult and complications are not uncommon even when the patients are under medical surveillance. Their report concerns 50 cases of surgically induced hypoparathyroidism seen since 1927.

The onset of clinical hypoparathyroidism occurred most often in the week following operation. Tingling, paresthesias and numbness of the fingers and toes were most common. Carpopedal spasm, Trousseau's, Chvostek's and Erb's signs soon appeared. Tightness and stiffness of other muscle groups, a feeling of restricted inspiration and expiration, hyperventilation and laryngospasm were less frequent and late. Of the 50 patients 33 had Chvostek's sign, 30 tingling, 29 muscle cramps, 23 carpal spasm, 25 Trousseau's sign, 20 pedal spasm, 14 numbness, 9 paresthesias, 8 stiffness, 6 each disorientation or twitching, 5 convulsions, 4 ringing in ears, 3 each hyperventilation or Erb's sign and 2 each laryngospasm, dysphagia or anxiousness.

Vitamin D 50 000-200 000 units daily and calcium orally (calcium lactate powder 5-15 Gm daily) should be started as soon as diagnosis is made. The correct doses are determined by following the patient's course and serum calcium and phosphorus levels. Vitamin D is available in 50 000 unit capsules; the dose is 1-4 capsules daily orally; its cost is $0 03-0 12 cents daily and it is effective when used with increased calcium and decreased phosphorus intake. Calcium lactate powder provides the high calcium intake: 1 teaspoon equals 3 Gm; dosage is 1 teaspoon three times daily and at bedtime in drinks other than milk; its cost is $0 008 daily and it has the advantage of providing high calcium ingestion for absorption and for combining with phosphorus as insoluble $Ca_3(PO_4)_2$, which is lost in the stool, thus maintaining a low serum P.

Late complications in the 50 patients with postoperative hypoparathyroidism were cataract in 10, convulsions in 7, mental deterioration in 3, psychosis in 2 and cardiac insufficiency and death in 1 each.

In a patient who has recently had thyroid surgery the appearance of these symptoms and signs is pathognomonic of *parathyroid* insufficiency. Laboratory determinations showing depressed serum calcium and elevated serum phosphorus levels and decreased or absent calcium excretion in the urine confirm the diagnosis. Further confirmation is pro-

the disease frequently have extensive necrosis in the pituitary gland particularly in the anterior lobe but there have been no previous reports of pituitary deficiency diagnosed ante mortem

Man 21 had apparently recovered from acute hemorrhagic fever but there was residual inability to concentrate the urine with polyuria anorexia occasional vomiting and malaise Physical examination revealed a slender asthenic pale man The white blood cell count was 12 800 with 64% lymphocytes and hematocrit 36 Sedimentation rate was slightly elevated Maximal specific gravity was 1 009 peak concentration 1 010 and phenolsulfonphthalein excretion was 52% total 35% in 30 minutes

A prolonged clonic convulsion with urinary incontinence occurred on the 92st day of illness Endocrine function was then evaluated Circulating eosinophil count ranged from 440 to 660/cc and was uninfluenced by ACTH or epinephrine Urinary 17 ketosteroid excretion was 4 1 and 1 7 mg /24 hours on two occasions and 11 oxysteroid excretion 0 026 Gm /24 hours No diuresis followed an increased water load Fasting blood sugar content ranged between 63 and 84 mg /100 ml

Therapy was started with 10 mg desoxycorticosterone in divided doses daily with increased dietary salt Within a day or two his appetite increased he gained weight and the weakness was ameliorated On the sixth day of therapy he had a generalized convulsion and died

At autopsy the pituitary was grossly atrophied with old fibrosis and infarction microscopically Only a thin rim of chromophobe cells remained of the normal anterior lobe The posterior lobe showed slight compression atrophy and microscopic condensation fibrosis The adrenal glands were thin and exhibited lipid depletion of the cortex with scattered fibrosis of the zona fasciculata There was early atrophy of the thyroid and the testicular tubules showed maturation arrest of spermatogenesis In addition widespread vasculitis was present and there was evidence of patchy interstitial nephritis

The scarring of the pituitary in this patient can be ascribed to epidemic hemorrhagic fever on the ba is of the history and the pathologic changes The fibrosis of the anterior lobe was central similar to the necrosis of the pituitary in acute stages of this disease Pituitary destruction was sufficient to produce clinical panhypopituitarism *

The immediate cause of death was not demonstrable but the consistently low blood sugar content and the convulsion leading to death sugge t an acute hypoglycemic episode

• [This syndrome is rem n scent of postpartum necrosis of the pitu tary n that each occurs after a period of shock in a pat ent with altered vascular permeability Minor pituitary infarcts are quite common at autopsy but massive destruction such as is descr bed here can probably occur only

pathogenesis and treatment of various forms of bone disease that include so called resistance to vitamin D

Calcium and Phosphorus Metabolism in Gastrectomized Patients was studied by R Nicolaysen and R Ragard (Univ of Oslo) Calcium balance in man normally varies abruptly from one fortnightly period to another and a consistent negative balance for months may be followed by a consistently positive balance for months Most normal subjects adjust to low intakes of 400 500 mg Ca daily by improved absorption Calcium excretion remains fairly constant in any one subject for years but usually varies between 100 and 400 mg daily in different persons In some patients urinary calcium is reduced when intake is reduced and in others excretion remains constant

The 15 patients in this study were investigated for fortnightly periods For the reasons listed only substantial deviations from normal can be considered significant Absorption of calcium was clearly defective in many patients with gastrectomy probably due to excess fat in the intestinal contents Vitamin D deficiency may be partly responsible Urinary calcium in some patients was below the values found in normal persons but relatively high excretions were found in others Calcium excretion probably is dominated by endogenous factors Negative phosphorus balances observed may be in part due to defective calcium absorption and in part to loss of body protein

Patients who have had gastrectomy should receive liberal amounts of calcium and vitamin D The negative calcium balances observed in several patients with gastrectomy cannot continue long without serious consequences

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THE PITUITARY GLAND

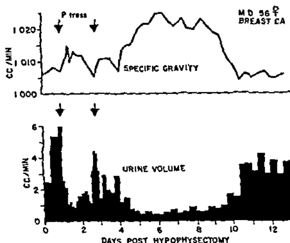
Panhypopituitarism Following Epidemic Hemorrhagic Fever I Clinical Features II Pathologic Anatomy A case is reported by Samuel J Zoeckler James A Orbison George H Wahle Jr and Donald G McKay[8] (U S Army Hosp Fort Belvoir Va) Patients who die in the acute stages of

(7) S and av J Clin & Lab I st 7 298 99 1955
(8) A Int Med 43 1316-1319 1320 1330 December 1955

as pitressin® tannate in oil an extremely reliable preparation for intramuscular injection

Analysis of Polyuria Induced by Hypophysectomy in Man is made by M B Lipsett J P Maclean C D West M C Li and O H Pearson[1] (Sloan Kettering Inst) who studied 42 patients who had hypophysectomy for advanced metastatic cancer

All the patients had relative polyuria postoperatively Those who did not have more than 3 cc /minute urine out



F g 112—Water xchang and spec f g ity f u n pat ent b h t ng normal terph se f llow g hypophysectomy (C urt y f L psett M B t l J Clin Endoc in L 16 183 195 F bru ry 19 6)

put during the first 24 hours still produced 1 500 3 000 cc during this period Polyuria often developed rapidly changing from 1 cc /minute to 5 10 cc in the course of an hour It began at varying times during the first 24 hours and time of onset may have been related to degree of operative trauma gradation in kidney response to circulating antidiuretic hormone or individual variations in its release In four patients periods of normal urine flow followed immediate polyuria and preceded the transition to permanent polyuria (Fig 112)

Permanent polyuria did not occur when only the portion of hypophysis beneath the diaphragma sellae was removed

(1) J C E docn 1 16 183 195 F bruary 1956

when pre existing vascular disease or altered pituitary metabolism has made the gland particularly susceptible to anoxia —Ed]

Neurosurgical Experiences with Diabetes Insipidus E H Botterell and W J Horsey[9] found 22 cases of diabetes in sipidus in the records of the Toronto General Hospital The cause was trauma in 7 tumor in 2 sarcoidosis in 1 and un determined in 12 Incidence of diabetes insipidus as a com plication of craniocerebral injury was found to be 0 44% The role of injury is well demonstrated by the following patients

CASE 1 —Man 18 hit by a truck sustained a linear fracture of the base of the skull but no basal fracture was seen on x ray examination Thirteen days after injury the urinary output began to rise It reached 13 700 cc /day and was accompanied by a heavy fluid intake Specific gravity of the urine fell from 1 012 to 1 001 The 24 hour exchange of fluids was reduced to less than 2 500 cc by intramuscular injection of 1 cc pitressin® in oil every 3 days He continued to require hormone therapy

CASE 7 —Man 54 survived a severe craniocerebral injury for nine hours but during a 2½ hour period he excreted 900 cc of pale urine Autopsy revealed recent hemorrhage in a cystic space in the in fundibular process of the hypophysis

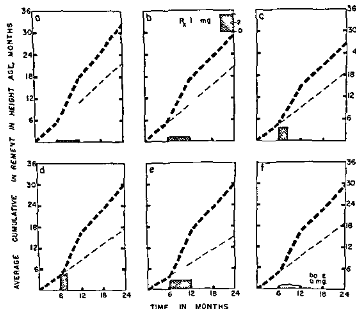
All but one case of diabetes insipidus following trauma showed a lag of several days between time of injury and onset of symptoms The average delay was about eight days in the four cases in which the interval was measured The recorded latent period that precedes onset of diabetes may be due to failure to recognize polyuria and polydipsia in an un co operative restless or semicomatose patient who is inconti nent and unable to request fluids On the other hand it may correspond to the delay in development of diabetes insipidus following experimental lesions of the supraopticohypophysi al tract in animals with the continued liberation of stored antidiuretic hormone by the denervated gland It is note worthy that the patient with hemorrhage into the neuro hypophysis (Case 7) had polyuria on the day of his injury The course in this instance could be compared with that of animals in which the entire neurohypophysis is ablated re sulting in immediate total diabetes insipidus

Removal of tumors from the suprasellar region and from the pituitary fossa often fails to control diabetes The most effective management is to give pitressin® in amounts suf ficiently large to meet the requirement All patients so treated in the present series were improved It is available

(9) N ol gy 5 449 460 July 1955

preceded by injection of 25 mg progesterone to induce a normal flow subsequently followed by regular spontaneous cycles

Use of Methyltestosterone to Stimulate Growth Relative Influence on Skeletal Maturation and Linear Growth Edna H Sobel C Stanley Raymond Karl V Quinn and Nathan B



F g 113 — A g m l t ea n h ght g pl tt d t x month t l f h d g g oup (S ct th ough) d f t g p (f) I t pt d d g nal l h t p t n t polat f th h ght g g bse l th t l p d D l d l d t f t tm t h w by th h t h d ea h ect (C t y f b l E H J Cl E d l 16 41 248 F b ry 1956)

Talbot (Harvard Med School) studied 13 boys and 14 girls aged 5½ 10 who were short for their ages

Small doses of testosterone 5 mg daily were as effective in promoting growth as the usual therapeutic amounts of 10 20 mg daily Larger doses evoked no greater growth acceleration In the six months before treatment increments in height age and skeletal age were fairly similar with an average of 4 7 months and 4 3 months respectively Thus the children were developing more slowly than the average

( ) J Cl E doc L 16 41 48 F bru y 1956

Polyuria is not a criterion for the completeness of hypophysectomy Diabetes insipidus persisted throughout periods of cortisone withdrawal Patients with hypophysectomy did not excrete as much water daily as occurs in diabetes insipidus but they responded to hypertonic saline in a grossly abnormal manner If some function of the hypothalamic-pars nervosa system remains hypertonic saline should elicit a response This did occur in three patients indicating that the small remnant of functioning pars nervosa could release extra antidiuretic hormone in response to extreme hypertonicity

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GROWTH WEIGHT GAIN AND NUTRITION

Treatment of Excessive Growth in the Adolescent Female In the absence of an expanding eosinophilic adenoma of the anterior pituitary growth in adolescence rarely reaches the stage of gigantism but excessive growth in the adolescent female is likely to raise social and economic problems which can elicit serious emotional disturbances

Max A Goldzieher[3] (New York) treated 14 girls whose growth was excessive using estrogen or combinations of estrogen and testosterone Ages ranged from 9 to 16 and the initial height was 59¼ 72 in Treatment was started if a height of 66 in had been reached and full growth potential remained (epiphysial lines open) or if height was 4 in or more above the average for the age even though less than 66 in Treatment was stopped when the patient had not grown for three months and the epiphyses were fused

Medication consisted of 1 6 mg estradiol monobenzoate every five days by injection 2 mg stilbestrol daily or 2 5-4 0 mg premarin® daily Testosterone was added only after the first two or three months when the initial growth spurt had subsided Treatment varied from three months to five years and the average growth increment during the time of treatment was 2 in Further growth did not occur

The only *side effect* was on *menstruation* In two patients excessive bleeding necessitated injection of 50 mg testosterone propionate and ergotamine maleate orally When therapy was eventually terminated withdrawal of estrogen was

(3) J Clin E docrinol 16 249 252 February 1956

more than expected on the basis of the control rate of maturation Thus although skeletal height increased the skeletal age increased even more Figure 114 depicts this graphically The downward slope of the lines emphasizes the progressively greater increase in skeletal maturation

The observations suggest that testosterone inhibits growth despite its immediate action of stimulating increase in height With prolonged use of testosterone skeletal maturation may be augmented to the point where distinct stunting might be induced This is commonly observed in boys with true sexual precocity and in children with adrenal virilism

Effect of Estrogen on Water and Electrolyte Metabolism II Hepatic Disease Estrogens normally inactivated by the liver have a salt retaining action in animals In human liver disease certain clinical features are best explained by increased estrogen activity This same factor may lead to sodium retention according to John R K Preedy and Elsie H Aitken[4] (London)

Daily estrogen administration to patients with hepatic cirrhosis and ascites increased the rate of weight gain water balance was more positive and urinary excretion of chloride and sodium was decreased (Fig 115) The potassium output was not significantly altered Average retention during the estrogen period was 325 mEq Na 218 mEq Cl and 1 950 ml water Average weight gain was 2 06 kg The same dose of estrogens in normal subjects was without significant effect

In patients with hepatic cirrhosis without ascites average retention was 126 mEq Na 99 mEq Cl and 266 ml water Average weight gain was 0 74 kg In patients with ascites but no hepatic disease portal hypertension without hepatic disease and biliary obstruction estrogens caused no significant alteration in NaCl or water metabolism Results were similar to those obtained in normal subjects

Increased abdominal tension or congestion of the inferior vena cava can cause decreased renal clearance However this is probably not the mechanism of estrogen retention since the patients who had ascites and hepatic cirrhosis had normal renal function Portal hypertension itself is not important since in several patients with portal hypertension but

(4) J Cl I t. 35 430-442 Ap 1 1956

When receiving testosterone all the children had accelerated growth rate regardless of the dosage (Fig 113) The average increment in height age was 12 1 months for those receiving 5 mg daily and 13 2 months for those receiving 20 mg daily during the six months Two years after the beginning of the study (one year after the end of testosterone

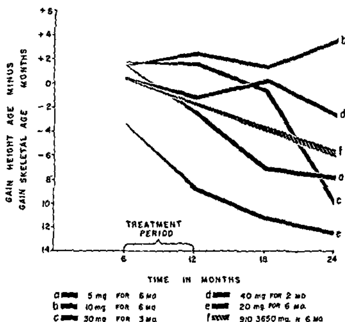


Fig 114—Average cumulative gain in height age minus gain in skeletal age plotted at six month intervals for each dosage group (a through e) and for the average of the entire group (f) Although in Group e skeletal age was increasing more rapidly than height gain the control period there was correlation between this phenomenon and the relative degree of skeletal maturation induced by testosterone (Courtesy of Sobel, F H et al J Clin E docr nol 16 241 248 February 19 6)

therapy) the average total height age increment was 30 months Therefore the average increase over the expected increment was 11 months and most of this gain occurred within the period of treatment

In each dosage group increase in skeletal maturation was noticeable and exceeded the increase in skeletal height The greatest increase occurred in children receiving the most testosterone Even after testosterone was discontinued skeletal maturation continued to accelerate The average skeletal age increment in the two year period was 35 6 m

183

more than expected on the basis of the control rate of maturation Thus although skeletal height increased the skeletal age increased even more Figure 114 depicts this graphically The downward slope of the lines emphasizes the progressively greater increase in skeletal maturation

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(4) J Cl I t. 35 430-44 Ap 1, 1956

no hepatic disease response to estrogens was within normal range

Estrogens cause NaCl and water retention in patients with hepatic cirrhosis and ascites probably because the hormone

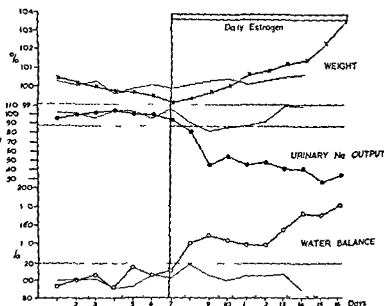


Fig 115 —Effect of e t g dm t at d l w ght u ry sod o tput a d wate b la e i c hos s w th te Co t l pe od da 1 6 t gen pe od day 7 w d Each point p ts da ly a x f gt p p e ed p r e tage of o t l pe od m W ter bala q al da ly t tal w t t ke le s u na y output Ho nt l nt upt d l d n t 9 o f d c l m t fo nt l period f ch cla of bse t R ult n o m l g up a e nse t d fo om par n (cont us l) (Court y of P dy J R K l A tken E H J Cl n In t 35 430-44 Apr l 1956)

is not inactivated as rapidly as in normal subjects Thi is not entirely due to hepatocellular damage since biopsies showed more damage in the cirrhotics without ascites than in those with fluid retention Estimated hepatic blood flow is reduced in cirrhosis of the liver Probably the reduced hepatic circulation is an important factor in the abnormal response to estrogens

Weight Gain from Simple Overeating I Character of Tissue Gained *Ancel Keys Joseph T Anderson and Josef Brozek* (Hastings Minn State Hosp) induced 20 men to over

(5) M tabol m 4 4 7-43 September 1955

eat for six months while on constant activity The subjects were stabilized mental patients with schizophrenia co operative and without physical or metabolic abnormality Body composition was repeatedly studied by thiocyanate dilution space and in 10 men by underwater weighing corrected by simultaneous residual air measurement Calculations involved known densities of fat and extracellular fluid the limits for density of cells (presumably cytoplasm) and possible glycogen changes

In the 20 men total weight gain was 211 6 kg and extra cellular fluid increased 50 5 L of thiocyanate space Converted to estimated true extracellular fluid by factor 0 7 and expressed as weight the increased fluid accounted for 17% of the total weight gain The net gain exclusive of extra cellular fluid was a mixture of cellular material and fat Only two thirds of the weight gain could have been fat and about 4% protein

Previously the difference in body composition between thin and fat men was considered entirely adipose tis ue 85% pure fat and 15% water These figure usually cited are a misinterpretation of the data of Bozenraad who reported 7 9 46 2% (average 15%) water in excised adipose tissue he made no analysis of fat content Weight gain other things being equal implies a greater muscular mass to carry the extra weight and a greater circulatory volume to supply it Extracellular fluid remains proportional to total body mass and in all ordinary men one sixth of the gross body weight can be considered extracellular fluid

Tissue mass gained by starved men in rehabilitation was different from that gained by well fed men who simply ate to excess Whereas two thirds of the gain in well fed men was pure fat in starved men the gain was only 10 20% fat Tissue mass gained by these well fed men was 13 15% extracellular fluid 61 64% fat 0 1% glycogen the remainder being cells The composition of this obesity tissue was independent of the weight gain over the range 2 5 22 5 kg gain The mean energy value of the tissue gained was 6 180 calories/kg These values were lower in cells and higher in fat than that of tissue gained by men fed after prolonged severe undernutrition

The gain of cells contributes to basal metabolism in the f d state Lean body mass is not absolutely constant

even in a given individual since the proportions of cells extracellular fluid and bone change with the nutritional state

Study of Interrelationship of Energy Yielding Nutrients Blood Glucose Levels and Subjective Appetite in Man was done by Jeffrey H Fryer Norman S Moore Harold H Williams and Charlotte M Young[6] (Cornell Univ) The hypothalamus has been identified as the site of a so called appetite center Mayer and his co workers have suggested that the factor which gives information to the hypothalamus as to recent food intake is not the absolute blood glucose level but the available blood glucose level as measured by the arteriovenous glucose difference or delta glucose

The authors tested the satiety value of the three major energy yielding nutrients carbohydrate fat and protein in 12 overweight subjects using isocaloric reducing diets and

SUBJECTIVE RESPONSE TO REDUCING DIETS*

DIET	RANKED CHOICE OF DIETS FOR SATIETY VALUE		
	First	Second	Third
Low carbohydrate	5	3	0
Low fat	2	4	2
Low protein	1	1	6

*Two subjects ranked all three diets equal two made no adequate assessments

attempted to relate changes in satiety value to the glucostatic theory of the regulation of food intake as proposed and elaborated by Mayer and associates After an adaptation period to each diet capillary and venous blood samples were obtained from each subject for 24 hours during which meals conformed to the diet of the preceding three weeks

The subjects ranked the low carbohydrate diet the most satiating and the low protein diets the least with the low fat diet holding an intermediate position In general the difference between the diet low in carbohydrate and that low in fat was not great (table) This indicates that the protein component of a diet is more important than either fat or carbohydrate components in satisfying appetite at least in a situation of caloric deficit

Examination of the capillary and delta glucose curves for the four reducing diets used (Fig 116) shows no consistent

(6) J Lab & Clin Med. 45 684-696 May 1955

correlation of the height of the glucose response with any single dietary component However the low carbohydrate diet which had the highest satiety value also showed the lowest ranked mean values for both capillary blood glucose and delta glucose Conversely the diets low in protein with

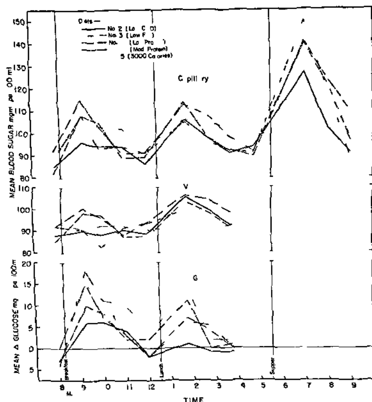


Fig 116—M cap ll y v a d d lt gl l ls ll d t (C t y of F y J H t l J Lab & Cl M d 45 684 696 M y 1955)

comparatively lower satiety value had the highest ranked mean value for capillary blood glucose and the mean delta glucose value exceeded that found in the low carbohydrate diet by a significant amount

Changes in blood glucose levels are associated with complex parallel changes throughout the metabolic pool and it

may be that the over all balance between metabolites within this integrated system provides the humoral mechanism controlling appetite through the mediation of the hypothalamic centers Such a theory transfers the emphasis from blood glucose which stands, so to speak on the carbohydrate portal of the metabolic pool to the dynamic equilibrium existing on the final common pathway of metabolism This would adequately explain Mayer s findings while allowing for differential factors compatible with the apparent superiority of protein in providing satiety

Night Eating Syndrome Pattern of Food Intake among Certain Obese Patients was studied by Albert J Stunkard William J Grace and Harold G Wolff (New York Hosp Cornell Med Center)[7] in *23* obese females and *2* obese males aged 18 56 A new syndrome was observed Characteristics were consumption of large amounts of food during the evening and night following the evening meal sleeplessness and negligible food intake at breakfast The syndrome was fully developed in 16 patients and was present with minor variations in the other 4

The syndrome influenced the results of and incidence of unsatisfactory reactions toward weight reduction programs Of the 20 patients exhibiting the syndrome only 11 had ever lost more than a third of excess weight During previous and current efforts at weight reduction 10 severe complications occurred including bronchial asthma bleeding peptic ulcer psychotic depressive reaction and disabling emotional illness The last complication was seen in 8 of 11 patients who previously had lost more than a third of excess weight

The etiology of the syndrome is unknown Its characteristics do not reveal whether the mechanisms involved in its pathogenesis are primarily physiologic or psychologic The authors suggest that the syndrome represents a response to stress of a type peculiar to certain obese patients and that it is intimately related to the pathogenesis of obesity

Lethal Anorexia Nervosa with Hypokalemia is described by R E Siebenmann[8] (Univ of Zurich)

Woman 27 was hospitalized because of severe cachexia Living on a reducing diet and cathartics she reduced her weight from 127 6 lb at 18 to 83 6 lb at 25 Clinical examination revealed severe weight loss and compensated aortic insufficiency No endocrine disturbances were

(7) Am J Med 19 78 86 July 1955
(8) Schweiz med Wchnschr 85 468 471 May 14 1955

found During hospitalization the daily caloric intake dropped from 500 calories/day to 200 300 preterminally The urine was sugar free but showed increased amounts of albumin Nonprotein nitrogen level was 32 mg total protein 7.2 Gm potassium 2 0 mEq /L and chlorides 109 mEq /L Intensive potassium therapy failed to raise the potassium level which two days before death was 2 1 mEq /L ECG was indicative of hypokalemia

Autopsy revealed severe emaciation the patient weighing only 58 3 lb 48% of her ideal weight The breasts were normal The heart and the kidneys were overweight the former probably due to ventricu



F g 117—T b l f o m l w dth p h l m h w hyd p d gen t d w llen ften t d] g ell (Court y f S he m R E Shw ız m d W h sch 8 468-471 M y 14 1955)

lar hypertrophy associat d with syphilitic mesaortiti The myocardi um showed old and recent necrotic foci with primary degeneration of mu cl fibers The kidneys revealed gross and micro copic severe nephrosis but no inflammatory or vascular change Changes were most severe in the proximal end of the tubules collecting tubules were intact (Fig 117) Similar myocardial and renal alterations due to hypokalemia have been observed by other authors in human beings as well as in animals

These findings indicate that severe hypokalemia of long standing may lead to morphologic changes

Hypokalemia may be due to lack of intake insufficient ab sorption and increased excretion of potassium by the bowel or to increase in intracellular pota sium (diabetic acidosis)

and in renal excretion In the latter two conditions hypo kalemia does not cause renal tubular degeneration

• [Several other cases were reported by Rosser *et al* (Schweiz med Wchnschr 85 465 1955) In these cases hypokalemia of severe degree was associated with alkalosis in some instances —Ed]

Relation of Nitrogen Retention to Nitrogen Intake in Adults with Post Traumatic Malnutrition was investigated by Bruce T Forsyth Margaret E Shipman and Irvin C Plough[9] (Walter Reed Gen l Hosp) In most patients at least two levels of nitrogen intake were employed while ca loric intake was kept constant Balance periods were long enough to allow for re equilibration of nitrogen metabolism after changes *in dietary nitrogen In all patients fecal nitro* gen analyses were performed All subjects were well into the anabolic phase of convalescence with major wounds healed and *no significant infection*

The authors first determined the time needed to reach a steady urinary nitrogen excretion at three ranges of nitrogen *intake* In each case the preceding ad lib diets *provided ni* trogen intakes estimated at 0 2-0 25 Gm N/kg /day (i e 1 2 1 5 Gm protein/kg /day) With diets containing 0 6 *Gm or more urinary nitrogen excretion continued to rise* through the fourth day of the new diet and then leveled off With diets containing 0 4 0 59 Gm N/kg /day urinary ni *trogen was relatively constant after the second day Urinary* nitrogen excretion was nearly constant from the start with diets containing 0 16-0 39 Gm N although variability was *greater during* the first two days

The coefficient of correlation between nitrogen intake and nitrogen retention (Gm /kg /day) was 0 74 with $p<0\,01$ *The regression equation was* $Y = 0\,016 + 0\,19X$ *where* Y is nitrogen retention and X is nitrogen intake The data show no tendency for the fraction of nitrogen intake retained to decrease at high levels of intake (Fig 118)

With nitrogen intakes ranging from 0 16 to 0 85 Gm / kg /day no diminished efficiency in the use of dietary nitro gen was evident at the higher levels of intake Nonprotein calories appeared to have a relatively small effect on nitro gen retention The rate of nitrogen storage *did not seem re* lated to the degree of malnutrition

The desirability of increasing nitrogen retention in mal

(9) J Clin In est 34 1653 1661 Novembe 1955

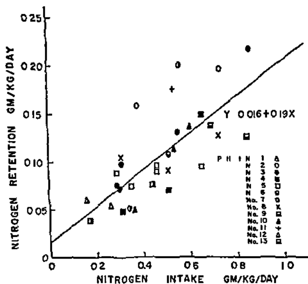


Fig 118—R l t n f n t gen t t on to netr g i tak (Courte y of For yth B T et l J Cl I st 34 1653 1661 N vembe 1955)

nourished patients has been stressed by many authors It would appear from the present study that increa ed nitrogen retention may be more readily accomplished by an increase in dietary nitrogen rather than an increased caloric intake provided caloric intake is adequate initially The authors found no apparent parallelism between estimated loss of lean body mass and rate of nitrogen storage

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METABOLIC DISEASES

Acute Idiopathic Porphyria Complicating Pregnancy J P O Dwyer[1] (General Hosp Sunderland England) reports a case This comparatively rare disease is characterized by attacks of abdominal pain vomiting stubborn constipation and red or brown discoloration of the urine However the urine may remain unpigmented even during an acute attack Occasionally psychotic changes appear The disease has a

(1) J Ob t & Gyn ec B t Emp 62 437-440 J 1955

tendency to mimic an acute condition of the abdomen Men strual disturbances particularly amenorrhea are common In some cases lower motor neurone paralysis may occur Spontaneous remissions often occur and the disease may remain latent for years

Woman 23 was hospitalized three times during one pregnancy On the first admission because of attacks of lower abdominal pain vomiting and constipation and because ectopic pregnancy was sus pected exploration was performed which revealed normal internal genitalia in the 10th week of pregnancy Second admission was for hyperemesis Attacks of crampy abdominal pain backache and uri nary frequency had again appeared and the physician had noticed blood in the urine on two occasions The third admission was for pain and weakness in the limbs and hysterical attacks The urine re vealed porphyria On liver extract vitamin B and demerol® (pethi dine) she improved

Six months after her first hospitalization she was delivered normal ly of twins which survived Their urine contained no porphyrins She remained symptom free though the porphyrinuria persisted

This and previous reports suggest that the total experience of childbearing may have a beneficial effect on the porphyric patient

As has been reported, barbiturates and laparotomy dur ing the acute phase of porphyria may cause progression of symptoms and a rapidly fatal termination

Renal Function in Case of Acute Porphyria with Hyper tension was studied by P Cottier and E Blaser (Univ of Bern)

Man 28 given 8 tablets of pyridacil for an influenza like illness developed acute abdominal porphyria about a week later After pass ing reddish brown urine he was hospitalized He was dehydrated and had persistent abdominal pain tachycardia and mild but sustained hypertension (150/100) Apart from mild hypokalemia the only sig nificant abnormal findings were 542 µg coproporphyrin and 80 µg uroporphyrin in a 24 hour urine sample Flocculation tests suggested slight impairment of liver function but results were normal on dis charge nine weeks later

Renal function studies on the 14th day of illness revealed a normal clearance of thiosulfate (signifying glomerular filtration rate) low renal plasma flow (60% of normal) and a distinctly high filtration fraction (30 1%)—results indicating increased resistance in the ef ferent arterioles Despite the normal filtration rate urinary output amounted to only about 800 ml daily this pointed to a high rate of tubular reabsorption of water *However other tubular functions ap peared normal* since extraction of sodium para aminohippurate by the kidney amounted to 96 3%

(2) H l et m d act 22 50 508 November 1955

Renal plasma flow was still low on the 24th and 36th days at which time the glomerular filtration rate was also just belo v normal During the intervening 10 days there was moderate diuresis attributed to a change in tubular function Blood pressure returned to normal on about the 35th day and excretion of porphyrins had fallen virtually to zero by the 25th day All renal function tests yielded normal results on the 44th day and again on the 75th

The delay between fall in blood pressure and return of normal renal function suggests an extrarenal origin for the hypertension of porphyria

Acute Intermittent Porphyria with Acute Abdominal Findings and Palpable Mass According to Wesley Furste and Perry R Ayres[3] (Ohio State Univ) acute intermittent porphyria may simulate the acute form of appendicitis cho lecystitis bowel obstruction and other surgical abdominal conditions

Woman 40 had severe constant boring low back pain and lower abdominal sharp crampy pain for one month after three days of diar rhea An enema was required every other day for a bowel movement and she was nauseated and vomited on several occasions Physical examination revealed a pulse rate of 108 and a flat undistended slightly tender abdomen with hyperactive normally pitched peri staltic sounds The only abnormal laboratory finding was a white blood cell count of 10 850 which increased to 16 000 Serum amylase was 49 Somogyi units On the second hospital day the diagnosis of intermittent porphyria was confirmed by urine tests and spectro photometric studies of urine extracts revealed pathologic concentra tions of coproporphyrins and/or uroporphyrins

Numerous findings indicated an acute surgical abdomen Severe abdominal pain persisted an x ray of the abdomen showed an oval shaped mass of barium in the right lower abdominal quadrant and a mass was palpated in thi area on the morning after admission Re peat barium enema x ray studies indicated the possibility of an intesti nal diverticulum with barium trapped in the diverticulum The pa tient was prepared for surgery but the mass could no longer be palpated An x ray of the abdomen revealed that the barium mass had moved to the left transverse colon After multiple enemas and cathartics the barium was spontaneously passed

Alkaptonuria Report of 12 Cases William J Martin Lau rentius O Underdahl Don R Mathieson and David G Pugh[4] (Mayo Clinic) report that of 12 patients with alkapto nuria seen from 1927 to 1953 8 had ochronosis In alkapto nuria the urine darkens on standing or on addition of alkali due to homogentisic acid one of the alkapton bodies Ochronosis is a metabolic condition which results in deposi

(3) A M A Arch S g 72 4 6 430 M h 1956
(4) A I t. M d 4 105 1064 M y 1955

tion of alkapton bodies in certain tissues Spontaneous alkaptonuria usually is inherited

In patients with alkaptonuria homogentisic acid which is a catabolite of tyrosine and phenylalanine is not metabolized to acetone by an enzyme or catalyst, as in normal persons but appears in the blood and urine Alkaptonuria may be asymptomatic or cause secondary signs, but in severe or long standing cases it may induce ochronosis which may be apparent from pigmentation of the parts of the body where homogentisic acid is deposited *The ochronosis may be asymptomatic or may induce ochronotic or alkaptonuric osteoarthritis due to degeneration of the joint cartilages Thus* ochronosis is characterized by the triad darkening of the urine on standing pigmentation and arthritis

In 7 of the 12 patients the main complaint was backache in 6 of the 7 x ray examination of the spinal column showed changes characteristic of ochronosis Diabetes had been considered at one time in four patients because the homogentisuria was mistaken for glycosuria On questioning the patient may relate that his underclothing has been stained brown from birth This report was made by seven patients *Ocular ochronosis characterized by brown or gray pigment in the sclera midway between the margin of the cornea and the outer or inner canthus was seen in five patients* The cartilage of the ear may be bluish or black *thick and inflexible and the ochronotic portions cannot be transilluminated* This condition was observed in seven of the ochronotic patients Brown or black pigment may be distributed on the nose and cheeks in the shape of a butterfly

The joints most often affected by ochronotic arthritis are those of the spinal column shoulders knees and hips The spine becomes rigid there is thoracic kyphosis and the normal lumbar lordosis is reduced or accentuated X ray examination reveals degeneration flattening and marked calcification of the intervertebral disks *Fusion of the anterior aspects of several of the vertebral bodies in the thoracolumbar region may be seen*

Freshly voided urine is not unusual in color if it is acid if alkaline it appears brown *When a specimen is exposed to air* it gradually becomes brownish black Addition of alkali causes darkening in seconds Homogentisic aci [illegible]

cally related to photographic developers and urine which contains it will immediately blacken exposed photographic film

Osteogenesis Imperfecta Tarda with Hyperuricemia and Gout Georgia E Allen Fred B Rogers and John Lansbury (Temple Univ) found that the character of the gouty attacks in three patients was altered by the abnormal nature of the connective tissue substrate The patients men between 22 and 59 had true gouty arthritis Hyperuricemia was noted in two All three responded to colchicine therapy but the response was either partial or brief as might be expected in the tophaceous stage of gout It was not clearcut and dramatic as would be expected in the early stage of acute gouty arthritis The long term response to antigout therapy was also exceedingly poor in all three cases

Prolongation of attacks of acute gouty arthritis and their poor response to therapy may possibly be related to the defect in or paucity of hyaluronate containing tissues the fundamental defect in osteogenesis imperfecta Thus if there is a paucity of the fixed hyaluronate tissues there may also be an insufficiency of free hyaluronates in the body fluids Such a deficiency would favor the precipitation of urates into the tissues since hyaluronates act as dispersing agents

The coexistence of osteogenesis imperfecta tarda with hyperuricemia and gout seems to be due to a chance genetic relationship

Some Observations on 520 Gouty Patients are reported by William C Kuzell Ralph W Schaffarzick W Edward Naugler Peter Koets Eldon A Mankle Beverly Brown and Barbara Champlin[6] (Stanford Univ) Gout is a syndrome characterized by recurrent attacks of painful acute arthritis a tendency to localized urate deposition chronic polyarthritis and possible renal insufficiency Though it has been described predominantly in men in this study 373 were males and 131 females About half the patients had chronic and half acute intermittent gout The most frequent age groups were the fifth sixth and seventh decades Only 9% of the females and 17% of the males were under age 40

Other painful musculoskeletal disorders were frequently found osteoarthritis bursitis and peritendinitis being the

(5) Am J M S 230 30 32 J ly 1955
c. D 2 645 669 Dec mber 1955

commonest Coincidence of ankylosing spondylitis and gout, 4 8% for males and 3% for females, was more than would be expected by chance Rheumatoid arthritis occurred in 5 4% of the males and 7 6% of the females Obesity was present in 50% of all patients, hypertension in 25 and 33 3% thyroid deficiency in 20 and 33 3% and cardiac disorders in 10 and 1 5% of the males and females, respectively

Diseases in the past considered prevalent among patients with gout were not prominent Lead poisoning had occurred in only one and renal stone was noted in only 5% of the males and less than 1% of the females Renal insufficiency was infrequent and ocular disorders were present in about 8% of all patients

Eighteen patients died Death was caused by myocardial infarction in 11 (61%) renal failure in 2 carcinoma in 2 and cerebrovascular accident pulmonary embolism and cardiac decompensation in 1 each A recent study of actuarial data of life insurance revealed no increased mortality in gout as compared with the general population

In view of the association of gout and obesity athero genic indices (index of coronary atherogenicity dependent on the ratio and total content of lipoprotein fractions) were determined in an unselected group of patients with gout Nine patients with tophaceous gout showed an average atherogenic index of 108 In six patients without tophi the average was 107 5 The upper limit of normal in the same age group is less than 80

Effective agents for treatment of acute gouty arthritis included colchicine ACTH demecolcine and phenylbutazone Local injection of hydrocortisone was valuable as an adjunct Less effective and often actually aggravating were cortisone hydrocortisone and prednisone orally Chronic gouty arthritis was apparently best managed by probenecid and phenylbutazone singly or in combination Phenylbutazone was the single most effective remedy for immediate termination of acute gouty arthritis prevention of acute exacerbations and control of chronic gouty arthritis

LIPID METABOLISM

Displacement of Serum Water by Lipids of Hyperlipemic Serum New Method for Rapid Determination of Serum Water is described by Margaret J Albrink Pauline M Hald Evelyn B Man and John P Peters[7] (Yale Univ) using the method of freezing point depression after adding known amounts of salt

Electrolyte concentrations in lactescent serums are mis leadingly low but are normal when determined after remov ing the insoluble lipids by ultracentrifugation or if values are expre sed in terms of serum water concentration In the pre ence of excessive serum fat electrolytes and other water soluble components may be so depressed that the patient s clinical status may be incorrectly evaluated The osmometric method is not influenced by hyperlipemia icterus or the presence of excess sugar or nonprotein nitrogen

In a patient with diabetic acidosis the original lactescent serum contained in mEq /L Na 102 5 and Cl 74 5 Osmo metric determination revealed Na 141 After removal of the insoluble lipids the same serum contained Na 135 and Cl 102 Repeated observations on another sample of serum re vealed that the lactescent serum contained total fatty acids of 526 mEq /L Na 103 and Cl undetermined The osmo metric value of Na was 142 mEq /L After centrifuging the subnatant contained total fatty acids of 33 Na 134 5 and Cl 100

For the accurate interpretation of serum sodium concen tration sodium must be expressed in terms of serum water This is even more important if the serum is markedly lac tescent especially because abnormal sodium concentrations are often found in diabetic acidosis and nephrosis diseases frequently associated with lactescence

• [Spur ous depression of electrolyte concentrations in patients with greatly elevated plasma l p d levels may lead to serious therapeutic mis takes The difficulty is likely to occur in diabetic acidosis in myxedema (see p 655) or in nephrosis among other conditions —Ed.]

Effect of Heparin on Distribution of Intravenously Ad ministered C^{14} Labeled Soy Bean Oil Emulsion in Rats was tudied by Gerald H Becker Theodore W Rall and Morton

(7) J Cl I est 34 1483 1488 Octobe 1955

I Grossman[8] (Fitzsimons Army Hosp Denver) Ii nously infused emulsions of fat were rapidly remove the blood of rats treated with heparin but rate of re was too fast for oxidation and gravimetric analyses *tissues were not sensitive enough to detect changes in* position following heparin

A tracer material C^{14} labeled soy bean oil obtainc *biosynthesis was injected as an emulsion in glucose* tween® 60 as emulsifying agent Half the rats receive mg heparin/kg 15 minutes before the emulsion wa jected

The amount of C^{14} lipid recovered from whole blood spleen was much less in heparinized than in nonheparini rats from the liver it was slightly increased in the forr and from the lung about the same in both The C^{14} lipid co tent of skeletal muscle small intestine and skin was higl in heparinized rats The C^{14} lipid fixation in these tissu was considered indicative of generalized C^{14} lipid fixatic Except in one instance respiratory CO contained high amounts of *C^{14} in heparinized animals* Though this a counted for only a small portion of the C^{14} removed fro the blood under the influence of heparin, apparently mor *C^{14}* lipid was presented to tissues to be available for oxida tion

The marked rise in C^{14} in the respiratory CO indicate that heparin speeds oxidation of injected fat emulsion Whether this is associated with a general rise in fat oxida tion or is a selective action on injected fat emulsion cannot as yet be decided Since postheparin plasma is lipolytic and tissues oxidize free fatty acid rather than triglyceride aug mentation of oxidation of injected fat emulsion by heparin may be due to increased rate of presentation of fatty acid to tissues

Transport of Lipids in Chyle It is thought that except for short chain fatty acids nearly all dietary fat is delivered from the intestinal tract to serum via the thoracic duct Chyle is a physiologic fluid rich in neutral fat which in turn has a pro found influence on the physical state of lipids in serum

Margaret J Albrink William W I Glenn John P Peters

(8) J Lab & Cl Med 45 786 791 My 1955

and Evelyn B Man[9] (Yale Univ) investigated the concentration and physical state of the lipids in chyle The lipids were divided into those present in the emulsified state causing the milky appearance of chyle and those present in clear solution Chyle was collected from nonfasting patients with chylothoraces or thoracic dust fistulas The chyle was universally lactescent Neutral fat was the chief component but cholesterol and phospholipid were present in varying concentrations All lipid components were present largely in the emulsified state and were removed by ultracentrifugation

Chyle obtained from two fasting dogs with thoracic duct fistulas was only slightly lactescent and contained relatively little neutral fat The cholesterol and phospholipid occurred almost entirely in the subnatant layer after centrifugation

It appears that newly formed water soluble lipoproteins are initially delivered to the thoracic duct probably via the liver lymph In the nonfasting state they are much richer in neutral fat than are the serum lipoproteins This discrepancy is ascribed to the rapid removal of neutral fat from the lipoprotein molecule by the peripheral tissues

The data support the concept of a lipoprotein molecule which is a stable protein cholesterol phospholipid complex designed to transport a highly labile rapidly removed component neutral fat from the liver to the peripheral tissues This shuttle system would continue until all the insoluble lipid particles temporarily deposited in the liver after a fat meal were removed The rate at which the liver disposed of the particles would depend partly on the rate at which existing lipoproteins were freed of the previous load of neutral fat thus becoming available to carry more fat

• [The levels and distribution of plasma lipids and lipoproteins are under the control of many factors The mechanism of handling alimentary lipemia described in the two previous articles is probably qualitatively similar to the handling of the hyperlipemia of diabetic acidosis described in the following article —Ed]

Hyperlipemias in Disorders of Carbohydrate Metabolism Serial Lipoprotein Studies in Diabetic Acidosis with Xanthomatosis and in Glycogen Storage Disease Felix O Kolb Oliver F de Lalla and John W Gofman[1] (Univ of Califor

(9) J Cl I t 34 1467 1475 S pt mbe 1955
(1) Met bol m 4 310 317 J ly 1955

mia) found considerable similarity in the lipoprotein transport derangement between glycogen storage disease and diabetic acidosis. Both disorders are characterized by inadequacy of carbohydrate utilization.

Both high and low density lipoprotein transport changes were studied during therapy for diabetic acidosis in a woman, 37, with severe diabetes for five years, poorly controlled by diet and insulin, and with xanthomas for about three months. Two patients with glycogen storage disease complicated by hyperuricemia and gout were also studied. Fasting blood serum specimens on all occasions of observation were grossly creamy in both patients. Lipoproteins of low and high density classes were studied ultracentrifugally.

At height of diabetic acidosis the low density lipoprotein distribution pattern had the following features: lower than normal S_f 0-12 level, elevated S_f 12-20 level, massively elevated S_f 20-100 level and even more massively elevated S_f 100-400 level. As diabetic acidosis was treated several important changes in lipoprotein distribution occurred. The S_f°100-400 concentration first dropped sharply with a concomitant rise in S_f 20-100, S_f 12-20 and S_f 0-12 levels. A few days later the S_f 100-400 level dropped still further, the S_f 20-100 level began to drop, but the S_f 12-20 and S_f 0-12 levels continued the upward trend in concentration. Still later, after two weeks of therapy of acidosis, the S_f°100-400 and S_f 20-100 levels continued to drop and the S_f 12-20 level began to fall. The S_f 0-12 level continued its upward trend in concentration. With further therapy all four classes of low density lipoproteins showed falls in concentrations toward those for matched controls. With control of diabetic acidosis xanthomas cleared completely. In the patients with glycogen storage disease most aspects of the lipoprotein findings were closely similar to those in diabetic acidosis.

The high degree of similarity in the lipoprotein transport derangement of diabetic acidosis and glycogen storage disease suggests that hyperglycemia per se is not the likely underlying factor but rather that a defect in carbohydrate utilization may be such a factor.

Exercise in Disposition of Dietary Calories. Regulation of Serum Lipoprotein and Cholesterol Levels in Human Subjects. George V. Mann, Katherine Teel, Olive Hayes

Ann McNally and Dorothy Bruno (Harvard Univ) evaluated experimentally the hypothesis that the magnitude of total caloric turnover in human subjects controls serum lipoprotein levels and disposition of the calories in the diet controls serum cholesterol level when excess of food calories is converted to body fat serum cholesterol level is high and when a caloric balance or deficit is present serum cholesterol level is low

Four medical students participated in a 10 week experiment During period A (one week) they were observed on ad lib food intake with the usual scholastic activity and while maintaining a steady body weight During period B (four weeks) caloric intake was doubled whereas fat intake was kept constant at control level the subjects maintained body weight within 5 lb of mean weight by strenuous physical exercise During period C (three weeks) they returned to control level of energy expenditure but high calorie and constant fat intake continued thus permitting deposition of body fat During period D (two weeks) they were restricted in food calories the exercise and dietary fat remaining constant to remove the fat deposited during period C

The young men consuming high fat diets were able to double the caloric supply without increasing serum lipid levels so long as excess energy was dissipated as exercise There was a suggestion of a downward trend of the serum cholesterol and lipoprotein levels during the period of high energy turnover These findings suggest that serum lipid levels are related to caloric balance of the body Increase of serum cholesterol phospholipid and beta lipoprotein levels that was associated with fat deposition in two of the three subjects confirms previous findings

Alpha lipoprotein levels were not significantly changed Beta lipoprotein levels were changed but appeared less sensitive to these influences than serum cholesterol levels Deposition of adipose tissue led to increase of the levels of both serum beta lipoprotein of the S_f0 100 classes and cholesterol Creatinine excretion which theoretically is a measure of body muscle mass was not a sensitive indicator

The author suggest that positive caloric balance over a

( ) N w E gl d J M d 253 349 355 S pt. 1 1955

long period elevates serum lipid levels and contributes to atherogenesis

* [Increased tissue demand for energy (i e fat) probably increases the passage of lipids out of the blood thus accelerating the process described. —Ed]

Effect of Essential Unsaturated Fatty Acids and Methionine on Hypercholesteremia was investigated by Seymour L Shapiro and Louis Freedman[3] (Yonkers N Y) who used hydrogenated fat safflower oil and methionine singly or in combination for the feeding of rats and observed their influence on cholesterol levels Safflower oil has a high content of unsaturated fatty acids since it consists up to 80% of linoleic acid The pattern of the experiment evident after

EFFECT OF % CHOLESTEROL DIET ON CHOLESTEROL LEVELS*

GROUP	% OF DIET			22 DAYS ON DIET SERUM CHOLESTEROL	AFTER 40 DAYS ON DIET PLASMA CHOLESTEROL
	HF	SO	M		
I	5	0	0 6	157(8)	207(11)
II	2 5	2 5	0 6	119(9)	135(11)
III	0	5	0 6	114(8)	118(10)
IV	5	0	0	212(8)	197(8)
V	0	5	0	222(9)	2[illegible]6(10)

Numbe f t d ated pare th HF nd t s hyd ogenated fat SO ffowe l d M m thi C t ol h le t l 86(8)

the cholesterol fed animals had been on the diet for only 22 days (table) showed the lowest cholesterol levels in the groups receiving the safflower oil supplemented with 0 6% methionine

The consensus of various estimates leads to a value of the order of 1 5% by weight of the total diet as linoleic acid/day as the requirement for an essential noncalorigenic function

There have been many reports in the literature on arteriosclerosis in which the use of diets containing significant quantities of the essential unsaturated fatty acids resulted in an impressive fall in serum cholesterol

On the other hand results of previous experiments suggest that while the essential unsaturated fatty acids have served their noncalorigenic function excess intake causes a breaking point in their protective action and yields higher cholesterol levels

The authors feel that the incorporation of about 2 5% by

(3) Am J Phy ol. 181 441 445 M y 1955

weight of the total diet of vegetable oil high in content of sterically required isomers of the essential unsaturated fatty acids is important in the design of diets intended for treatment and prevention of atherosclerosis

• [Since certain lipids (especially cholesterol esters and phospholipids) have a high content of unsaturated essential fatty acids failure to supply these acids in adequate quantities may produce dislocations of the plasma lipid concentrations and of lipid utilization These observations extend and confirm the data of Ahrens *et al* (1955 56 YEAR BOOK p 674) —Ed]

Influence of Gonadal Hormones on Protein Lipid Relationships in Human Plasma was studied by Ella M Russ Howard A Eder and David P Barr[4] (New York Hosp Cornell Med Center) Plasma proteins were separated by the method of Cohn in which alpha lipoproteins are recovered in fraction IV + V + VI and beta lipoproteins in fraction I + III

Administration of ethinyl estradiol estrone sulfate or diethylstilbestrol tended to correct the pathologic protein lipid relationships in survivors of myocardial infarction and completely restored normal patterns in many The most constant and characteristic effect was a change in the distribution of cholesterol with a higher percentage of the total appearing in fraction IV + V + VI The dose was 1 mg ethinyl estradiol or 15 mg estrone sulfate orally a day or 1 mg diethylstilbestrol the first day increased by 1 mg daily for eight days Longest period of continued administration was six months and maximal effects were attained about six weeks after the initial dose When continued for long periods the effect did not diminish No tolerance or resistance developed

After the hormone was discontinued the concentration of cholesterol rose rapidly in fraction I + III and often exceeded pretreatment levels Within two or three weeks the values returned to a pattern almost identical with that before treatment

The gonadal effects of the hormones were evident in all patients (mostly men) Loss of sexual desire and potency were noted early The breasts enlarged and impotence was complete within four weeks The patients were restless dissatisfied and depressed No consistent effect on anginal pain was noted

In six patients with primary hypercholesterolemic xan

(4) Am J Med. 19 4 24 J ly 1955

long period elevates serum lipid levels and contributes to atherogenesis

• (Increased tissue demand for energy (i e fat) probably increases the passage of lipids out of the blood thus accelerating the process described. —Ed]

Effect of Essential Unsaturated Fatty Acids and Methionine on Hypercholesteremia was investigated by Seymour L Shapiro and Louis Freedman[3] (Yonkers, N Y) who used hydrogenated fat safflower oil and methionine singly or in combination for the feeding of rats and observed their influence on cholesterol levels Safflower oil has a high content of unsaturated fatty acids since it consists up to 80% of linoleic acid The pattern of the experiment evident after

EFFECT OF 3% CHOLESTEROL DIET ON CHOLESTEROL LEVELS*

GROUP	% OF DIET			22 DAYS ON DIET SERUM CHOLESTEROL	AFTER 40 DAYS OF DIET PLASMA CHOLESTEROL
	HF	SO	M		
I	5	0	0.6	157(8)	207(11)
II	2.5	2.5	0.6	119(9)	135(11)
III	0	5	0.6	114(8)	118(10)
IV	5	0	0	212(8)	197(8)
V	0	5	0	222(9)	256(10)

Numb f t d c e d pa e the HF d te hyd gen ted fat SO affl wer o l d M neth Cont ol ch l ste l 86(28)

the cholesterol fed animals had been on the diet for only 22 days (table) showed the lowest cholesterol levels in the groups receiving the safflower oil supplemented with 0.6% methionine

The consensus of various estimates leads to a value of the order of 1.5% by weight of the total diet as linoleic acid/day as the requirement for an essential noncalorigenic function

There have been many reports in the literature on arteriosclerosis in which the use of diets containing significant quantities of the essential unsaturated fatty acids resulted in an impressive fall in serum cholesterol

On the other hand results of previous experiments suggest that while the essential unsaturated fatty acids have served their noncalorigenic function excess intake cau e a breaking point in their protective action and yields higher cholesterol levels

The authors feel that the incorporation of about 2.5% by

(3) Am. J Physiol 181 441-445 May 1955

seven patients four had angina pectoris two had xanthoma and one a child had nephrosis The patients were placed in a metabolic unit and studied during three periods During the first period they received a diet adequate in carbohydrate protein minerals and vitamins but containing less than 0 25 Gm fat/24 hours In the second period the diet was kept isocaloric and isonitrogenous and 49 Gm vegetable fat/day was added In the third the diet of the second period was enriched with 30 60 cc of a sitosterol preparation daily

On extreme fat restriction (first period) the greatest decline of the total serum cholesterol was seen in patients with the highest initial values While the serum cholesterol decreased in all patients a steady decline was seen only in two

Four patients who received sitosterol for periods up to 35 weeks after discharge showed no alteration of serum cholesterol with doses of 15 30 Gm /day Three other (ambulatory) patients who received 15 30 Gm /day and were on diets of choice showed no change in serum cholesterol for periods of 3 20 weeks The preparation used produced gastrointestinal irritation in three out of seven patients sometimes rather promptly more often after days or weeks of use

There was no correlation between the course of the serum cholesterol values and the pattern of stool cholesterol excretion in the individual patient Neither was there any consistent difference between the first and second period as judged by mean daily stool excretions Finally the mean daily excretion values of stool cholesterol for the group were almost identical 0 25 Gm for the first period and 0 24 Gm for the second The addition of sitosterol did not alter plasma or stool cholesterol These figures are at variance with the earlier theory according to which diets free of fat and cholesterol produce a reduction of serum cholesterol by preventing resorption of biliary cholesterol

Essential Hyperlipemia is reported by R A Joske[6] (Melbourne) in one man and seven women aged 30 63 The clinical features varied Five patients had a family history of cardiac disease and one of cholelithiasis Skin nodules were present in four patients and tendon nodules in one Four had hepatomegaly and one splenomegaly while five had pancreatitis and two cholelithiasis Vascular disease was present *in two in one of whom status* anginosus developed A prob

(6) M J A tral 1 8 6831 J 4 1955

thomatosis results were similar to those in patients who had had myocardial infarctions but normal patterns of protein lipid relations were not established In two patients *with nephrosis the changes were in the same direction but* were insignificant

Methyl testosterone exerted the opposite effect exaggerating the chemical abnormality in survivors of myocardial infarction and producing an abnormal protein lipid balance in patients with previously normal patterns When estrogenic and androgenic hormones were given simultaneously the estrogen effects were modified or obliterated It was not definitely established that testosterone effects were modified by estrogens

These observations may be significant in the pathogenesis of athero clerosis and indicate a chemical reason for the relative immunity of young women to the complications of this disease Although estrogens clearly eliminate chemical abnormalities in protein lipid balance which may be regarded as detrimental more extensive clinical studies are necessary before they can be considered useful in prevention of atherosclerosis or in treatment of its complications

• [Certain attempts to prevent atherosclerosis have been based on the assumption that it is a metabolic disease The preceding articles indicate that some of the abnormalities commonly associated with atherosclerosi (and possibly contributing to its development) may be prevented or postponed by eating a diet with adequate unsaturated fatty acid content exercising appropriately and in extreme cases feminizin the patient with exogenous estrogen These measures aim at adjusting the total plasma lipid pattern toward normal without pecific interests in any single component In the following article the use of sitosterol as a specific anti cholesterol agent is evaluated The applicability of such agents is dubious since there is serious doubt that athero clero is is a disease of metabolism of cholesterol as di tinct from other lipids —Ed]

Effect of Varying the Intake of Dietary Fat and the Ingestion of Sitosterol on Lipid and Lipoprotein Fractions of Human Serum Sitosterol the principal sterol in soy beans has been described as causing a reduction in the expected increase in blood *cholesterol when added to the diet of choles*terol fed rabbits and likewise as having the ability to lower the blood chole terol in human subjects when added to their usual diets Several studies have described a reduction in blood cholesterol with sharp restriction of dietary fat

Charles F Wilkinson Jr Edwin Boyle Raymond S Jackson and Martin R Benjamin made metabolic studies of

(5) Metabol sm 4 30 309 J ly 1955

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able pituitary lesion and mild diabetes mellitus were observed in one patient Lipemia retinalis was not encountered

The pathogenesis of the abdominal pain which is often present is still uncertain It is usually severe and frequently intermittent and is felt in the upper abdomen on either the right or left side In the present series it was consistent with a diagnosis of pancreatitis in all patients in whom it occurred The pain may be sufficiently severe to cause difficulty in the differential diagnosis of upper abdominal pain due to such lesions as perforated peptic ulcer

In all patients the total serum lipid content was elevated at some stage of the disease up to 900 mg /100 ml or more Four patients also had hypercholesterolemia Apart from hyperlipemia due to increase of neutral fats there was no consistent pattern in the laboratory findings The sedimentation rate was elevated in three of the patients in whom it was measured There was no consistent abnormality in results of liver function tests Liver biopsy was performed in two patients In one it confirmed the diagnosis of intercurrent acute viral hepatitis and in addition there was a diffuse fine fatty change in the cytoplasm of parenchymal cells In the other patient on a low fat diet for some months the biopsy showed no abnormality Cholecystograms were normal in five patients Hypoglycemic episodes occurred in one

A low fat diet did not invariably reduce the blood lipid content and a prolonged course of heparin in one case of status anginosus affected neither clinical nor biochemical findings

• [Essential hyperlipemia is not explicable at present on the basis of theoretic concepts of lipid tran port outlined above Much in the field of lipid metabolism remains to be explained —Ed]

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